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Peri-procedural bridging with low molecular weight heparin in patients receiving warfarin for venous thromboembolism: A pediatric experience

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Abstract

INTRODUCTION—The incidence of venous thromboembolism (VTE) in children appears to be increasing, and warfarin remains one of the few standard anticoagulants used for secondary VTE prevention. When invasive procedures are required in adults with high TE risk who are receiving warfarin, low-molecular weight heparin (LMWH) bridging is recommended, based mainly upon observational evidence; in children, no such studies have been published. We sought to determine the risks of recurrent TE (both VTE and arterial TE [ATE]) and major bleeding with peri-procedural LMWH bridging in children receiving warfarin for VTE.

METHODS—Children (age ≥ 21 years of age at the time of bridge) receiving warfarin for VTE and undergoing a standardized clinical care protocol for peri-procedural LMWH bridging were enrolled and followed in an institution-based prospective inception cohort study at Children's Hospital Colorado between March 2006 and February 2012. Outcomes were assessed at 30 days post-procedure, and followed International Society on Thrombosis and Haemostasis guidelines.

RESULTS—Seventeen children comprised the cohort, with a total of 23 bridging episodes. Median age at bridging episode was 17.5 years (range, 12 to 21 years). In 22% of bridging episodes, indication was for major surgery. Median duration of LMWH administration prior to procedure was 6 days (range, 4–10 days); median duration off anticoagulation peri-procedurally was 1.5 days (range: 1–2 days). The risks of major bleeding, recurrent VTE, and ATE at 30 days post-procedure were 4.3% (1/23), 0% and 0%, respectively.

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CONCLUSIONS—This study provides important preliminary data on safety and efficacy of perioperative LMWH bridging for adolescent VTE patients receiving warfarin. Larger collaborative pediatric studies are warranted to substantiate these findings and to investigate prognostic factors of bleeding and recurrent TE in this setting.

INTRODUCTION

The peri-procedural management of patients on chronic oral anticoagulant therapy, especially vitamin K antagonist therapy such as warfarin, is a common clinical problem estimated to affect approximately 250,000 adult patients annually in North America.[1] In patients with high risk of recurrent thromboembolism (TE) off anticoagulation, warfarin is discontinued several days prior to procedure, and bridging therapy with a short-acting anticoagulant (typically low-molecular-weight-heparin [LMWH], and less commonly unfractionated heparin or fondaparinux) is used to transitionally maintain anticoagulation during the period in which the international normalized ratio (INR) is sub-therapeutic. The bridging anticoagulant is then stopped prior to procedure, resumed post-procedure along with warfarin, and maintained until the INR is once again therapeutic on warfarin.[2] Although this approach appears from observational studies to have low risks of major bleeding and recurrent TE, trials of peri-operative bridging therapy in adults receiving warfarin for atrial fibrillation and/or prosthetic heart valves are being conducted to determine whether bridging is superior to complete anticoagulant withdrawal.[3,4]

While the magnitude of the problem of peri-procedural anticoagulant management is not as well established in children when compared to adults, it is clear that warfarin remains a frequently utilized agent for venous TE (VTE) therapy in the pediatric setting,[5] particularly among teens and those patients in whom a prolonged course of anticoagulation appears warranted (e.g.: spontaneous-onset VTE; recurrent VTE; antiphospholipid antibody syndrome (APS); severe inherited thrombophilia state such as homozygous protein C, protein S, or antithrombin deficiency). Yet, there are no published studies of peri-procedural anticoagulant bridging in children. We therefore undertook to systematically evaluate outcomes of a standardized clinical care protocol for peri-procedural LMWH bridging in children receiving warfarin for VTE, by means of a single-institutional prospective inception cohort study. We hypothesized that the risks of major bleeding and recurrent TE are low with this management paradigm.

METHODS

Subjects and clinical care protocol

Following the approval of the Colorado Multiple Institutional Review Board, and with written informed consent (and assent as appropriate), children (age ≥ 21 years of age at the time of bridge) receiving warfarin anticoagulation for VTE and undergoing a clinical care protocol for peri-procedural LMWH bridging were enrolled and followed in an institution-based prospective inception cohort study at Children's Hospital Colorado between March 2006 and February 2012. The bridging protocol is given in Figure 1. The bridging regimen was enoxaparin at an age-specific treatment dose of 1.0–1.5 mg/kg/dose subcutaneously twice-daily. Dosing followed an electronic medical record (EMR)-based anticoagulant dosing and monitoring policy and procedure established by the senior author and colleagues and fulfilling JCAHO 3E requirements. This policy, and hence the clinical bridging protocol, employs age-grouped dosing that reflects the increased mg/kg dosing requirements with decreasing age in children, based upon previous institutional enoxaparin dose-finding experience targeting anti-Xa levels of 0.5–1.0 U/mL [6], and supported by recently published data [7]. For teens weighing >100kg, a dose of 1mg/kg was used. As is the case more broadly for standard-of-care use of any anticoagulants as secondary VTE prevention in

childhood VTE, LMWH is not approved by the U.S. Food and Drug Administration for an indication of bridging therapy for perioperative VTE prevention of patients on warfarin. Anti-Xa levels were not routinely performed within the clinical protocol for bridging with enoxaparin, but were to be performed (along with INRs) in the instance of bleeding complications.

Data collection

Baseline characteristics and treatment data were systematically collected on the following: age at bridge; gender; diagnosis of renal insufficiency; clinical risk factors for qualifying VTE; inherited thrombophilias; time interval from qualifying VTE to bridge; indication for long-term (>6 months) warfarin (if applicable); bridge indication; duration of LMWH administration during bridge; and duration off-anticoagulation during bridge. Diagnosis of renal insufficiency was collected at time of cohort enrollment by medical history obtained and verified by review of the patient's problem list within the EMR; the diagnosis was verified as active via supporting documentation of an elevated serum creatinine for age within 1 month prior to bridging episode. Diagnostic imaging for qualifying VTE consisted of compression ultrasound with Doppler, magnetic resonance venography, or conventional contrast venography, as previously described [8]. Comprehensive thrombophilia testing consisted of assessment for: anticoagulant deficiencies; the factor V Leiden and factor II G20210A polymorphisms; elevated homocysteine concentration, factor VIII activity, and lipoprotein(a); and antiphospholipid antibodies, as also described previously [9]. Inherited thrombophilia was defined as the presence of the factor V or factor II polymorphisms or confirmed anticoagulant deficiencies (protein C activity < 40 U/dL, free protein S antigen < 40%, antithrombin activity < 60 U/dL on two separate venipunctures at least 6 weeks apart, in the context of a family history of same or genetic confirmation of a known mutation). In accordance with the ISTH SSC guidelines for bridging studies [2], bridging indications were classified with regard to peri-procedural bleeding risk, as major versus minor procedures. Major procedures consisted of cardiothoracic and orthopedic surgeries, open abdominal/pelvic surgeries, and other surgeries typically lasting greater than 45 minutes (not including anesthesia induction and recovery periods).

Major bleed events and recurrent symptomatic TE events were uniformly ascertained at 30 days post-procedure, as the primary outcome of interest. Major bleeding was defined in accordance with ISTH SSC criteria for pediatric outcome reporting [10] as overt bleeding with a fall in hemoglobin of >2g/dL in a 24 hour period, central nervous system bleeding, fatal bleeding, or bleeding requiring surgical intervention in an operating suite to achieve hemostasis. Symptomatic recurrent VTE was defined as new DVT or PE with associated clinical signs/symptoms, in accordance with ISTH SSC criteria for pediatric outcome reporting. Symptomatic arterial thromboembolism (ATE), including arterial ischemic stroke, were tracked separately from VTE.

Statistical analysis

Analytic methods consisted of descriptive statistics. Distributions of continuous data were summarized by medians with observed ranges. Categorical data were summarized as frequencies with corresponding percentages.

RESULTS

Among 19 children who met eligibility criteria, 17 provided consent/assent for study participation, and comprised the present cohort. Four subjects underwent more than one bridging episode during follow-up, yielding a total of 23 bridges. Table 1 provides summary data on clinical characteristics, bridging LMWH, and outcomes. Median age at bridging

episode was 17.5 years (range, 12 to 21 years). Sixty-five percent of subjects were female. Inherited thrombophilias consisted of heterozygous factor V Leiden in two subjects and heterozygous protein C deficiency in an additional two. Specific indications for bridging episodes are detailed in Table 2. Renal insufficiency was present in one subject, consisting of mild chronic renal insufficiency due to congenital reflux nephropathy with residual scarring. Because estimated Creatinine clearance was >60 mL/min at time of bridging episode, no adjustment in enoxaparin frequency was made, although he was given a dose of approximately 1mg/kg rather than the usual 1.25 mg/kg for age 12-<18 years, due to weight >100kg (see also footnote, Figure 1).

During the 30 day post-procedural follow-up period for primary outcome ascertainment, one major bleeding event occurred, consisting of a subcapsular renal hemorrhage associated with a decline in Hgb of > 2g/dL in a 24 hour period in a child undergoing renal biopsy; spontaneous tamponade of the bleed was permitted to occur, without need for surgical intervention or infusion of blood products. Anti-Xa was unfortunately not performed as recommended in the clinical bridging protocol for instances of bleeding complications; however, the bleed was noted >24h after the last dose of enoxaparin, and INR had been verified as normal pre-operatively, at 1.07. This episode yielded an incidence of one major bleed in 690 patient-days, or a risk of 4.3% (1 in 23) at 30 days post-procedure. There were no symptomatic recurrent VTE or ATE events at 30 days post-procedure (incidence, 0 in 690 patient-days; risk, 0% [0 in 23]).

DISCUSSION

The present study provides unique prospective observational evidence on outcomes of a standardized clinical care protocol for treatment-dose LMWH bridging in pediatric (specifically, adolescent) VTE patients on warfarin therapy. It revealed a symptomatic recurrent VTE risk of 0% (0/23) at 30 days post-procedure in a cohort of patients who were mostly bridged >3 months following qualifying VTE event, many of whom were nevertheless at heightened *a priori* risk of recurrent VTE due to clinically-meaningful thrombophilia states, including APS and heterozygous anticoagulant deficiencies. There were also no ATE events. This work also determined a major bleeding risk of 4.3% (1/23) at 30 days post-procedure, which is not high in a peri-operative context. Hence, this study provides preliminary data suggestive of good safety and efficacy of perioperative LMWH bridging for pediatric VTE patients receiving warfarin.

Despite current consensus-based recommendations for LMWH bridging therapy in adult patients at high risk for TE [1], evidence for standardized bridging regimens is of low-quality, and notably not yet supported by randomized controlled clinical trials. In addition, most observational data has focused on patients with cardiac/arterial indications for warfarin therapy. The findings of this prospective study in pediatric VTE are consistent with those of recent observational studies of LMWH bridging in adult VTE. In a single-institutional prospective cohort of nearly 500 patients at the Mayo Clinic, in which 78% of patients had qualifying VTE >3 months prior to bridge, the 3-month risks of recurrent TE and major bleeding were 2.0% and 2.8% [11]. Similarly, a multicenter North American registry of LMWH or UFH bridging therapy led by Spyropoulos and colleagues demonstrated risks of recurrent TE and major bleeding of 0.9% and 3.4% among 230 patients with VTE.[12] Strengths of the present study include its utilization of both bridging study reporting guidelines [3] and pediatric VTE trial reporting guidelines [9] from the ISTH SSC, its prospective inception cohort design, and the derivation of its findings from a standardized clinical care protocol for LMWH bridging that is closely adheres to the only existing recommendations for LMWH bridging (albeit pertaining to adults). Its inclusion of children undergoing minor procedures, for which adult recommendations suggest to consider no

withdrawal of anticoagulation, is justified by the vulnerability of the pediatric population, in which a conservative approach toward minimizing bleeding risk (via transitioning off-warfarin) was clinically deemed most appropriate. While it can be argued that warfarin could have been withheld without LMWH bridging in this cohort, all patients were receiving warfarin anticoagulation based on a perceived high risk of recurrent VTE (i.e., were either within 3 months of qualifying non-spontaneous VTE, within one year of qualifying spontaneous VTE, or had a persistent potent thrombophilia state); hence, it was judged clinically appropriate to minimize time off-anticoagulation and potential for life-or limb-threatening VTE, particularly in the setting of a vulnerable pediatric population.

The main limitation of this work is the study's sample size which, while smaller than prior LMWH bridging cohorts in adult VTE, is nevertheless the largest and only such study reported in pediatrics. In addition, the uniformity of the clinical bridging protocol between major and minor procedures is both a limitation and a strength. Given the lack of prior pediatric bridging outcomes data and the vulnerability of the pediatric population, we employed a very conservative approach with a full week off warfarin and full anticoagulant coverage with therapeutic enoxaparin during this period, with the exception of one day after warfarin discontinuation and another day pre-operatively. If the present findings suggesting favorable outcomes are substantiated in a larger cohort, evaluation of a shortened bridge in further studies would be warranted. Lastly, this cohort was representative of adolescent patients, and hence its findings should not be extrapolated to younger children. Notwithstanding these limitations, the present prospective study provides important preliminary evidence on safety and efficacy of standardized peri-procedural LMWH bridging in adolescent children receiving warfarin for VTE. Larger collaborative pediatric studies are warranted to substantiate these findings, to evaluate whether a shortened bridge preserves efficacy in the setting of minor procedures, and to investigate prognostic factors of bleeding and recurrent TE in the perioperative setting.

References

1. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R. American College of Chest Physicians. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl):e326S–50S. [PubMed: 22315266]
2. Spyropoulos AC, Douketis DJ, Gerotziafas G, Kaatz S, Ortel TL, Schulman S. on behalf of the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Periprocedural antithrombotic and bridging therapy: recommendations for standardized reporting in patients with arterial indications for chronic oral anticoagulant therapy. J Thromb Haemost. 2012; 10:692–694. [PubMed: 22934291]
3. National Heart, Lung and Blood Institute. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); Effectiveness of bridging anticoagulation for surgery (The BRIDGE Study). Available from: <http://clinicaltrials.gov/ct2/show/NCT00786474>
4. Lawson Health Research Institute. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); PERIOP 2—a safety and effectiveness study of LMWH bridging therapy versus placebo bridging therapy for patients on long term warfarin and require temporary interruption of their warfarin. Available from: <http://clinicaltrials.gov/ct2/show/NCT00432796>
5. Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, Vesely SK. American College of Chest Physicians. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl):e737S–801S. [PubMed: 22315277]
6. Manco-Johnson MJ. How I treat venous thrombosis in children. Blood. 2006; 107(1):21–9. [PubMed: 16099882]

7. Bauman ME, Belletrutti MJ, Bajzar L, Black KL, Kuhle S, Bauman ML, Massicotte PM. Evaluation of enoxaparin dosing requirements in infants and children. Better dosing to achieve therapeutic levels. *Thromb Haemost.* 2009; 101(1):86–92. [PubMed: 19132193]
8. Goldenberg NA, Knapp-Clevenger R, Manco-Johnson MJ. Mountain States Regional Thrombophilia Group. Elevated plasma factor VIII and D-dimer levels as predictors of poor outcomes of thrombosis in children. *N Engl J Med.* 2004; 351(11):1081–8. [PubMed: 15356305]
9. Goldenberg NA, Durham JD, Knapp-Clevenger R, Manco-Johnson MJ. A thrombolytic regimen for high-risk deep venous thrombosis may substantially reduce the risk of postthrombotic syndrome in children. *Blood.* 2007; 110(1):45–53. [PubMed: 17360940]
10. Mitchell LG, Goldenberg NA, Male C, Kenet G, Monagle P, Nowak-Göttl U. Perinatal and Paediatric Haemostasis Subcommittee of the SSC of the ISTH. Definition of clinical efficacy and safety outcomes for clinical trials in deep venous thrombosis and pulmonary embolism in children. *J Thromb Haemost.* 2011; 9(9):1856–8. [PubMed: 21884565]
11. McBane RD, Wysokinski WE, Daniels PR, Litin SC, Slusser J, Hodge DO, Dowling NF, Heit JA. Periprocedural anticoagulation management of patients with venous thromboembolism. *Arterioscler Thromb Vasc Biol.* 2010; 30(3):442–8. [PubMed: 20139361]
12. Spyropoulos AC, Turpie AG, Dunn AS, Spandorfer J, Douketis J, Jacobson A, Frost FJ. REGIMEN Investigators. Clinical outcomes with unfractionated heparin or low-molecular-weight heparin as bridging therapy in patients on long-term oral anticoagulants: the REGIMEN registry. *J Thromb Haemost.* 2006; 4(6):1246–52. [PubMed: 16706967]

Day minus 7 prior to procedure: Stop warfarin

Day minus 6 through Day minus 2 prior to procedure: Administer enoxaparin 1.25 mg/kg* via subcutaneous injection twice-daily. Administer doses at the same time each day.

Day minus 1 prior to procedure: Administer enoxaparin 1.25 mg/kg* via subcutaneous injection in the morning only. Do not administer evening dose of enoxaparin.

Day of procedure: Do not administer morning dose of enoxaparin.

Day 1 post-procedure: Resume enoxaparin 1.25 mg/kg* via subcutaneous injection twice-daily at 24h post-procedure in the absence of peri-procedural bleeding complications and with clearance by the attending surgeon.

Day 2 through Day 7 post-procedure: Continue enoxaparin 1.25 mg/kg* via subcutaneous injection twice-daily, and resume once-daily oral warfarin at previous dose.

Day 7 post-procedure: Check INR; discuss result, the plan for subsequent warfarin, and suitability of discontinuing enoxaparin with anticoagulant pharmacist/attending hematologist.

Figure 1.

Standardized peri-procedural clinical care protocol for LMWH bridging in children on warfarin undergoing invasive procedures.

* Twice-daily therapeutic dosing as follows, as per institutional pediatric anticoagulant dosing and monitoring guideline: 0-<1 y.o.: 1.5 mg/kg/dose; 1-<6y.o.: 1.375 mg/kg/dose; 6-<18 y.o.: 1.25mg/kg/dose (1.0 mg/kg/dose if >100kg) ; 18 y.o.: 1.0 mg/kg/dose.

Table 1

Summary of patient characteristics, bridging therapy, and outcomes.

Gender	
Female	67%
Male	33%
Qualifying VTE event (indication [*] for warfarin)	
DVT +/- PE	80%
Isolated PE	20%
Inherited Thrombophilia	27%
Median (range) age at bridging episode	17.5 y (12 – 21 y)
Median (range) time from VTE diagnosis to bridging episode	9.6 mo (2.3 – 108 mo)
Period post-VTE diagnosis at time of bridging episode	
<30 d	0
30 d – < 3 mo	3
3 mo – < 1 y	9
1 y	11
Invasive procedure type	
Major surgery	22%
Minor surgery/other	78%
Median (range) bridging duration of LMWH pre-procedure	6 d (4 – 10 d)
Median (range) duration off all anticoagulation during bridging episode	1 d (1 – 2 d)
Indication [*] for long term anticoagulant therapy (> 6 mo; n=13) ^{**}	
APS	54%
Spontaneous VTE	46%
May Thurner	31%
Severe thrombophilia	8%
Outcomes (risks) at 30 d	
Major bleeding	4.3%
CRNM bleeding	0%
Recurrent VTE	0%
ATE	0%

^{*} No anticoagulants have an FDA-approved indication of VTE treatment in children. Hence, the term “indication” used here can be considered synonymous with “clinical justification”.

^{**} More than one indication existed in some patients; therefore, indications total greater than 100%.

Abbreviations: VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; LMWH, low molecular weight heparin; CRNM, clinically-relevant non-major.

Table 2

Summary of procedures for which LMWH bridging episodes (n=23) occurred in the cohort.

Procedure and type	N
Major surgery	
Resection of 1 st rib	2
Ileostomy/closure	2
Tendon transfer	1
Minor surgery/other	
Dental procedure (tooth extraction, pulpectomy)	7
Endoscopy (+/- biopsy)	2
Venography (+/- percutaneous intervention)	2
Central venous catheter placement	2
Flexible bronchoscopy (+/- biopsy)	1
Sinus surgery	1
Jejunum tube placement	1
Renal biopsy	1
Ingrown toenail removal	1