The safety and efficacy of use of low-molecular-weight heparin in pediatric neurosurgical patients

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OBJECT Low-molecular-weight heparins (LMWHs), mainly enoxaparin, offer several advantages over standard anticoagulation therapies such as unfractionated heparin and warfarin, including predictable pharmacokinetics, minimal monitoring, and subcutaneous administration. The purpose of this study was to determine the safety and efficacy of LMWHs in pediatric neurosurgical patients.

METHODS A retrospective study was performed with patients 18 years old or younger who were admitted to the Pediatric Neurosurgery Service at Texas Children's Hospital and treated with LMWH for either therapeutic or prophylactic purposes between March 1, 2011, and December 30, 2013. Demographic and clinical features and outcomes were recorded.

RESULTS LMWH was administered for treatment of venous thromboembolic events (VTEs) in 17 children and for prophylaxis in 24 children. Clinical resolution of VTEs occurred in 100% (17 of 17) of patients receiving therapeutic doses of LMWH. No patient receiving prophylactic doses of LMWH developed a new VTE. Major or minor bleeding complications occurred in 18% (3 of 17 children) and 4% (1 of 24 children) of those receiving therapeutic and prophylactic doses, respectively. All 4 patients who experienced hemorrhagic complications had other bleeding risk factors—i.e., coagulopathies and antiplatelet medications.

CONCLUSIONS LMWH seems to be safe and efficacious for both management and prophylaxis of VTEs in pediatric neurosurgery. However, pediatric practitioners should be aware of higher risk for bleeding complications with increasing doses of LMWH, especially in patients with preexisting bleeding disorders or concurrent use of antiplatelet agents.

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KEY WORDS low-molecular-weight heparin; enoxaparin; venous thromboembolism; deep venous thrombosis; anticoagulation; pediatric neurosurgery; hemorrhage; vascular disorders

PEDIATRIC venous thromboembolic events (VTEs) have become an emerging problem in Canada, with a 10-fold increase in incidence over the original estimates since the early 1990s, especially in tertiary care hospitals.¹ Plausible explanations for the rise in this population are related advances in tertiary pediatric health care that result in improved survival of critically ill children.¹ A more significant contributor is the increased use of central venous catheters in these children.¹³ VTE complications have been shown to independently increase inpatient costs and length of stay in young trauma patients.^{4,8}

Current therapy for management of VTEs in children is extrapolated from clinical experience and trials with adult patients. It usually consists of therapy with unfractionat-

ed heparin, low-molecular-weight heparin (LMWH), oral anticoagulants, or a combination of these medications.^{1,10} Poor venous access, unpredictable pharmacokinetics requiring serial monitoring, increased risk of bleeding related to primary disorders, and the influence of disease, diet, or medications adversely influence the safe usage of unfractionated heparin and oral anticoagulants, particularly in younger patients.^{5,6,10,16,19,20}

LMWHs offer several advantages over unfractionated heparin and oral anticoagulants in the management and prevention of VTEs in children,¹⁴ including predictable pharmacokinetics, subcutaneous administration, and minimal monitoring. However, there have been few studies in children assessing the pharmacokinetics, safety, and effi-

ABBREVIATIONS LMWH = low-molecular-weight heparin; VTE = venous thromboembolic event.

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TABLE 1. Children receiving prophylactic LMWH

Sex/Age (yrs)	Condition	Operation	Other Bleeding Risk	Type of Major Hemorrhage
F/15	Lumbar stenosis	L1–2 laminectomies		
M/17	Traumatic cervical spinal cord injury (C-5)	C4–6 instrumented fusion		
F/14	Traumatic cervical spinal cord injury (C-4)	C4–T3 instrumented fusion	Aspirin	
M/15	Thalamic tumor	Craniotomy, tumor resection	Hemophilia	Intracerebral
M/16	Rasmussen disease	Craniotomy, functional hemispherectomy		
F/16	AVM	Craniotomy, AVM resection		
M/12	Ewing sarcoma of spine	T2–4 laminoplasty, tumor resection		
F/18	Lumbar stenosis	L3–S1 laminectomies		
F/10	Lumbar spondylolisthesis	L5–S1 instrumented fusion		
M/16	Traumatic lumbar spine injury	T11–L2 instrumented fusion		
M/13	Lumbar epidural abscess	L4–S1 laminectomies		
F/13	Skull defect, remote head injury	Cranioplasty		
F/14	Neuromuscular scoliosis	T3–ilium fusion		
F/6	Intractable epilepsy	Functional hemispherotomy		
F/15	Medulloblastoma	Craniotomy for tumor		
M/15	L-1 burst fracture	T10–L3 posterior fusion		
M/3	Epilepsy	Functional hemispherotomy		
M/17	Lumbar stenosis	L2–S1 laminectomy		
M/16	Basal ganglia glioma	Craniotomy for tumor		
M/12	L5–S1 spondylolysis	L5–S1 posterior fusion		
M/16	C-3 osteoblastoma, myelopathy	C2–4 posterior fusion, tumor resection		
F/12	Midbrain pilocytic astrocytoma	Craniotomy for tumor		
M/17	Postlaminectomy kyphosis	C5–L3 posterior fusion		
M/14	Gunshot wound to head	Craniotomy for foreign object		

AVM = arteriovenous malformation.

cacy of LMWH.^{10,21} Furthermore, to the best of our knowledge, there have been no studies analyzing the safety and efficacy of LMWH in pediatric neurosurgical patients.¹¹

Methods

Patient Population

Institutional review board approval was obtained for this study from the Baylor College of Medicine. We retrospectively reviewed data on 2296 children operated on by the Pediatric Neurosurgery Service at Texas Children's Hospital between March 1, 2011, and December 30, 2013, and screened for those who were treated with the LMWH enoxaparin. Dosing alterations for therapy were made according to a published nomogram to maintain the antifactor Xa level between 0.5 and 1.0 U/ml. For prophylaxis, a target antifactor Xa range of 0.1–0.4 U/ml was used. Antifactor Xa levels were measured at 4 hours after the second or third dose, then weekly for the duration of treatment, per institutional protocol. In the event of bleeding or decreased renal function, antifactor Xa levels were measured more frequently.

One course of therapy was defined as daily administration of enoxaparin for a specific indication. Patients in whom therapy was briefly interrupted to perform invasive procedures were included.

Demographic Information

Weight, sex, age at diagnosis, and associated medical and surgical comorbidities were recorded for all patients. Likewise, data on treatment, such as duration of therapy, maintenance dosage, and dosing schedule, were recorded, and plasma antifactor Xa activity was noted.

Efficacy of LMWH therapy was assessed clinically in all patients. Efficacy was determined by the absence of symptomatic clot extension or recurrence in patients receiving therapeutic doses of enoxaparin and by the absence of symptomatic new clot formation in patients receiving prophylactic doses of enoxaparin. Major and minor bleeding complications were noted. Bleeding complications were considered major if a blood transfusion or surgical intervention was required to treat clinical bleeding, or if anticoagulant therapy was stopped because the responsible physician assessed the bleeding to be excessive. All cases of bleeding in the CNS and retroperitoneal space were classified as major hemorrhages. All other hemorrhages were classified as minor.

Results

Patient Population

There were 41 patients in the pediatric age group (less than 18 years of age) who received enoxaparin during the

TABLE 2. Children receiving therapeutic LMWH

Sex/Age (yrs)	Condition	Operation	Indication	Other Bleeding Risk	Type of Major Hemorrhage
M/3	Thoracic epidural abscess	T2–3, T-6, & T-12, laminectomies	DVT		
F/5	Cranial epidural abscess	Craniotomy, evacuation abscess	CVST	Thrombocytopenia	Palatal
M/0.2	Yolk sac tumor	Craniotomy, tumor resection	DVT		
F/2	Ventriculoperitoneal shunt infection	Craniotomy, evacuation abscess	DVT		
M/1	Moyamoya disease	Craniotomy, indirect revascularization	Arterial thrombosis	Aspirin	Intracerebral
M/16	Lumbar epidural abscess	L1–3 laminectomies, evacuation abscess	DVT		
F/10	Moyamoya disease	Craniotomy, indirect revascularization	Ischemic stroke	Aspirin	
M/3	Tuberculous meningitis	Ventriculoperitoneal shunt	CVST	Aspirin	Upper GI
M/1	Sickle cell w/ moyamoya disease	Indirect revascularization procedure	DVT	Aspirin	
M/9	Obstructive hydrocephalus	Endoscopic third ventriculostomy	DVT		
M/1	Closed traumatic brain injury	Cranioplasty & EVD	DVT		
M/0.3	Suprasellar pilomyxoid astrocytoma	Craniotomy for tumor	CVST		
M/0.3	X-linked chronic granulomatous disease	Craniotomy, resection of dural lesion	DVT		
F/17	Cerebral sinus thrombosis	Camino ICP monitor	CVST		
M/17	Lumbar decubitus ulcer	Vascularized wound flap	DVT		
F/11	Shunt infection	Ventriculoatrial shunt	DVT		
M/3	Atypical teratoid rhabdoid tumor	Ventriculoperitoneal shunt	DVT		

CVST = cerebral venous sinus thrombosis; DVT = deep venous thrombosis; EVD = external ventricular drain; GI = gastrointestinal; ICP = intracranial pressure.

study period. Of these patients, 17 received LMWH for management of VTEs, and 24 received LMWH for prophylaxis.

Demographic Information

The ages of children who received therapeutic doses ranged from 2 months to 17 years (median 3 years, mean 6 years). The chronological age of 4 patients (about 25%) was less than 1 year at the time of treatment initiation. The male/female ratio was 2:1.

The ages of children who received prophylactic doses ranged from 3 years to 18 years (median 15 years, mean age 14 years). The chronological age of all of these patients was older than 1 year at the time of treatment initiation. The male/female ratio was 3:2.

Comorbidities

An underlying coagulopathy or secondary anticoagulant medication administration was noted in 29% of patients receiving therapeutic doses and in 8% of patients receiving prophylactic doses of LMWH (Tables 1 and 2). LMWH was dispensed for the treatment of VTEs for reasons including venous sinus thrombosis, arterial thrombosis, deep venous thrombosis, and ischemic stroke (Table 3).

LMWH was dispensed for the prevention of VTEs in 24 patients. General indications for prophylactic anticoagulation were expected altered mobility for more than 48 hours in an older child (age less than 12 years or weight more than 65 kg) (Fig. 1). Specific indications included

general recovery after spine procedures with or without fusion (n = 11), spinal cord injury (n = 3), weakness after craniotomy (n = 5), bed rest for spinal fluid leak (n = 1), and traumatic brain injury (n = 3). Two younger patients who did not meet the indications based on age, weight, and mobility status received prophylactic anticoagulation for high-risk factors due to history of ischemic strokes related to protein C deficiency.

Treatment

Table 4 lists the doses observed to achieve target anti-factor Xa levels and the range of maintenance doses required. Conversion to warfarin was performed in 2 of 17 (12%) children receiving LMWH treatment, due to intolerance of daily needle injections.

Aspirin was used as an additional part of the anticoagu-

TABLE 3. Types of thrombotic disease in patients receiving therapeutic LMWH

Disease Type	No. of Patients
Overall no.	17
DVT/PE	11
Stroke	1
Dural sinus thrombosis	4
Arterial thrombosis	1

PE = pulmonary embolus.

FIG. 1. Our institutional guidelines for VTE risk assessment and prophylaxis against VTE in children. BID = twice daily; BMI = body mass index; CVC = central venous catheter; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; post-op = postoperative; SCD = sequential compression device; TED = thromboembolism-deterrent hose. Figure is available in color online only.

lation regimen in 4 of 17 children (24%) receiving LMWH treatment and in 1 (4%) receiving prophylaxis.

In the group receiving therapeutic doses, only 2 of the 17 children (12%) received LMWH for 20 days or less. The reasons for discontinuation of LMWH were as follows: conversion to warfarin ($n = 2$), resolution of clot or completion of therapy ($n = 14$), and major bleeding ($n = 1$). LMWH was briefly withheld but then reinitiated within 48 hours in both patients who had minor bleeding episodes.

In the group receiving prophylactic doses, 16 of the 24 patients (67%) received LMWH for 7 days or less. Three patients (13%) received indefinite continuation of the therapy for permanent impaired mobility. The reasons for discontinuation of LMWH were as follows: placement of an inferior vena cava filter ($n = 1$), major bleeding ($n = 1$), and mobilization of the patient ($n = 20$).

Twenty-one children (51%) received enoxaparin for therapy or prophylaxis only while being treated as hospital inpatients, and 20 (49%) received continued enoxaparin therapy in an outpatient setting.

Outcome

The efficacy of LMWH was assessed clinically in all patients, with patients who had symptoms of new or recurrent thrombosis undergoing objective radiographic testing. Documented progression of thrombosis occurred in none of the patients while receiving therapeutic LMWH, nor was there any symptomatic recurrence or incidence of new VTEs in those patients receiving prophylactic LMWH.

Complications

None of the patients in this study died while receiving LMWH. There were no correlations between duration of treatment, dosage schedule, or drug levels with the development of complications. Major bleeding occurred in 1 patient (6%) receiving therapeutic doses of enoxaparin, and minor bleeding occurred in another 2 (12%). The major bleeding consisted of an intracerebral parenchymal hemorrhage requiring surgical evacuation. All major or minor bleeding complications occurred in patients with coexisting coagulopathies (i.e., severe thrombocytopenia, aspirin use).

There was only 1 major bleeding complication (4%) that occurred among the 24 patients who received prophylactic LMWH. This was an intracerebral hemorrhage in a child who had previously unrecognized hemophilia.

Discussion

The advantages of LMWHs in adults have resulted in its increased off-label use in pediatric patients.⁴ Few studies describe the pharmacokinetics or use of LMWH in children,^{3,10,21} and no studies in the literature evaluate the safety and efficacy of LMWHs in the management of VTEs in pediatric neurosurgical patients.¹¹ Concerns regarding the use of unfractionated heparin followed by oral anticoagulants and the advantages of LMWH have resulted in growing interest in the use of LMWHs as alternative therapy in children.¹⁰

TABLE 4. Treatment characteristics for patients receiving LMWH

Dose (mg/kg/d)	No. of Patients
Prophylactic	
0.25	4
0.5	6
0.75	3
1	11
Therapeutic	
1.5	1
2	12
3	3
3.5	1

Patients in our study had characteristics similar to children described in other studies who had or were at risk for VTEs.^{2,10,15,18,21} There was a predominance of adolescents relative to younger children,²¹ and most children with VTEs had serious comorbidities, such as moyamoya disease or intracranial infections. Based on the higher rates of VTEs documented in adults, concern exists that the onset of puberty places adolescents at higher risk for VTEs than younger children.²¹ The heterogeneity and complexity of medical problems in our patients with VTEs reflect the current status of pediatric tertiary care hospitals.¹⁰ In contrast to children with deep venous thrombosis/pulmonary embolus, most children with arterial and venous thrombosis in the CNS were previously healthy.^{7,9,10}

In our study, there was considerable variation in the maintenance dose requirements for prophylaxis. Prophylactic dosing requirements were about 25%–30% of the therapeutic doses to achieve the target antifactor Xa range. There is a growing body of literature suggesting that an increased enoxaparin dosage in pediatric patients, particularly young patients, is required.¹ In a study by Punzalan et al.,¹⁷ the once-daily dosing is appealing for prophylaxis; however, the peak antifactor Xa level is in the therapeutic range, which may predispose children to an increased risk of bleeding when prophylaxis is the aim.¹² The safety and efficacy of twice-daily versus once-daily dosing for prophylaxis can only be assessed in a randomized clinical trial with clinical outcomes.¹²

The efficacy of LMWH was assessed by determining either if it prevented new or recurrent VTEs in patients with previous VTEs or if it prevented VTEs in patients at risk. Patients with symptoms of thrombosis underwent radiographic workup. Given the heterogeneity of this study cohort, both in terms of indications for anticoagulation and the duration and dosage of anticoagulation, routine radiographic assessment was not performed, which is consistent with standard pediatric and adult practice.¹⁰ No new or progressive VTEs occurred in children receiving prophylactic LMWH. These rates of new VTEs are similar to results from other clinical series involving children.¹⁰

Significant symptomatic bleeding occurred in 4 patients (about 10%). Three of these patients were receiving therapeutic doses of LMWH, and 1 was receiving prophylactic doses. The rate of major bleeding in our study was

similar to the rate of major bleeding in adult patients²² and children receiving unfractionated heparin.¹⁴

Conclusions

VTEs are underappreciated in the pediatric age group. LMWH represents an important advance. It offers a safe and effective form of anticoagulation in pediatric neurosurgical patients with or at risk for VTEs and, therefore, should be routinely used prophylactically or therapeutically in the at-risk pediatric patient population. However, caution should be applied to patients with preexisting bleeding disorders and those concurrently receiving antiplatelet agents, as major bleeding complications were shown in this subset of patients in our series.

All pediatric patients undergoing enoxaparin therapy should be monitored using antifactor Xa test measurement, as guidelines describe.³ An initial higher enoxaparin dose may be necessary to achieve target anticoagulation, particularly in young children. Further study is warranted in a randomized controlled fashion to compare LMWH with unfractionated heparin and oral anticoagulants in the treatment and prevention of VTEs in children in a pediatric neurosurgical service.

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