Intravenous Enoxaparin in Pediatric Burn Patients: A Case Series

Vonya N. Streetz, PharmD and Leslie K. Patatanian, PharmD

Patients with acute burns experience a hypercoagulable state that may necessitate the use of anticoagulants to prevent the complications of venous thromboembolism (VTE). Enoxaparin is a low molecular weight heparin that is commonly used for this purpose; however, the traditional SC route of administration poses potential limitations in the pediatric burn population. These include pain upon injection, increased anxiety, erroneous absorption and distribution, and difficulty in finding an administration site when burns encompass a large percentage of body surface area. As a result, the IV route of administration may be preferable in these patients. To date, a limited number of studies in critically ill pediatric patients have been performed. In this report, we present a case series of 3 pediatric burn patients who initially received SC enoxaparin and were transitioned to IV enoxaparin for VTE prophylaxis. The patients were 2, 8, and 10 years old. Burn involvement ranged from 8% to 75% total body surface area, and all patients had central line access. Adequate prophylactic low molecular weight heparin anti-Xa peak concentrations (0.1–0.3 international units/mL) were achieved with IV doses ranging from 0.35 to 0.5 mg/kg administered every 12 hours. No adverse effects, major bleeding events, or treatment failures occurred.

ABBREVIATIONS CHEST, American College of Chest Physicians; IV, intravenous; PICC, peripheral inserted central catheter; PICU, pediatric intensive care unit; SC, subcutaneous; TBSA, total body surface area; VTE, venous thromboembolism

KEYWORDS anti-factor Xa, burns, enoxaparin, intravenous, pediatrics

J Pediatr Pharmacol Ther 2019;24(5):456–461

DOI: 10.5863/1551-6776-24.5.456

Introduction

Thermal injuries have been demonstrated to alter coagulation pathway activity, ultimately inducing a hypercoagulable state and increasing the risk for thrombosis.¹ Venous thromboembolism (VTE) incidence in burn patients varies (0.2% to 43%) and is dependent on the specific patient subgroup being studied. Although the rate of thrombosis in pediatrics is lower than that in adults, 0.053% up to 6% in critically ill children versus 0.2% up to 23% in adults, the potential for thrombotic complications cannot be discounted.^{1–3} Monagle et al⁴ in the American College of Chest Physicians (CHEST) guidelines currently recommend the use of low molecular weight heparins for both primary and secondary VTE prophylaxis in pediatric patients. The majority of data are derived from studies that used enoxaparin with the Prophylaxis of Thromboembolism in Kids Trial targeting an anti-Xa range of 0.1 to 0.3 international units/mL measured 4 to 6 hours after SC administration.⁴ At this time, no formal guidelines detail specific pediatric populations in whom VTE prophylaxis is recommended or contraindicated. Institution-specific protocols and “Best Evidence Statements” have been created, with the presence of central venous catheters, trauma, and altered mobility beyond 48 hours being

listed as VTE risk factors requiring mechanical and/or pharmacological intervention.⁵

Enoxaparin is the most commonly used agent for the treatment and prevention of VTE in pediatric patients because of the drug’s more predictable dose response and reduced monitoring requirements compared with unfractionated heparin.³ However, the traditional SC route of administration may not be ideal in the burn population owing to potential pharmacokinetic alterations.⁶ Critically ill patients frequently undergo fluid shifts, renal insufficiency, and weight changes, which can affect the absorption and distribution of medications. Patients may also experience SC edema, vasopressor-induced peripheral vasoconstriction, or may simply lack sufficient SC tissue necessary for a SC injection if the burn encompasses a large percentage of body surface area.⁶ Exposure to SC injections also places children at risk for emotional distress. The IV route may be preferable but is only Food and Drug Administration approved for use in adults with acute coronary syndrome; its use within the pediatric population is limited to only a few studies.⁶ Given the paucity of information concerning IV enoxaparin not only in pediatrics but in burn patients as well, we reviewed our institution’s experience.

Methods

This study was approved by the INTEGRIS Baptist Medical Center's Institutional Review Board. The institution's electronic medical record system was searched to identify pediatric burn patients who received IV enoxaparin for VTE prophylaxis from November 27, 2016, through September 17, 2017. A total of 3 patients were identified. A retrospective chart review was used to collect data regarding patient demographics, burn wound characteristics, infection and ventilator status, renal function and hematological status, number of operative procedures and blood transfusions, and length of stay. Enoxaparin data collected included dose administered, route of administration, anti-Xa concentrations, duration of therapy, number and magnitude of dose adjustments needed, and occurrence of bleeding events. Intravenous enoxaparin doses were prepared in normal saline and administered over the course of 30 minutes through microbore tubing. Initial anti-Xa concentrations were routinely ordered to be drawn 4 hours after the end of the third infusion (goal of 0.1–0.3 units/mL). The same timing was used whenever a dose adjustment was made. Subsequent concentrations were ordered at the discretion of the provider and timed for 4 hours post infusion; concentrations were not determined in relation to a specific dose. Dose adjustments were made at the discretion of the healthcare team and did not follow a formal dosing algorithm. Generally speaking, however, the percent increase or decrease in the anti-Xa level desired corresponded to the percentage of the dose adjustment, such that a linear relationship was used. The assays used to determine anti-Xa concentrations were Rotachrom Heparin Kit (March 2015–August 2017) and STA-Liquid Anti-Xa (August 2017–September 30, 2017).

Results

The medical records of 7 pediatric burn patients were reviewed. Two patients each were excluded for lack of enoxaparin and lack of IV enoxaparin, respectively. A total of 3 patients were included in the analysis. No patient experienced a major bleed, defined as the occurrence of an intracranial hemorrhage, a hemorrhage resulting in ≥ 2 g/dL decrease in hemoglobin, or a hemorrhage requiring transfusion of ≥ 2 units (40 mL/kg) of blood products. No patient developed a VTE, as demonstrated per radiologic study, or had treatment failure, defined as the development of a new VTE, progression of a current VTE by ≥ 2 cm, or VTE recurrence. All enoxaparin doses administered and the anti-Xa concentrations achieved can be found in Table 1. Renal function and hematologic status are presented in Tables 2 and 3, respectively.

Patient 1. A 10-year-old, 34-kg Caucasian male presented with second- and third-degree burns to 75% total body surface area (TBSA). Upon arrival at the

PICU, a peripherally inserted central catheter (PICC) was placed, and the patient was started on mechanical ventilation. The patient was deemed to be at high risk for thrombosis as a result of a high-TBSA burn, inhalational injury, central line placement, ICU admission status, expected mechanical ventilation need of greater than 48 hours, an anticipated large number of operative procedures, and a high probability of acquiring infections. Prophylaxis was initiated with 1 mg/kg (40 mg) of SC enoxaparin dosed once daily. After the fourth dose, a peak anti-Xa level was obtained and was documented as supratherapeutic at 0.5 units/mL. Because of extensive injuries and the difficulty in finding adequate SC tissue in which to administer a SC injection, the patient was transitioned to IV enoxaparin at a dose of 0.5 mg/kg (17 mg) every 12 hours. While on this dose, anti-Xa concentrations ranged from 0.2 to 0.4 units/mL. The dose was not adjusted for the first elevated level of 0.4 units/mL but was decreased by 18% to 14 mg (0.41 mg/kg) every 12 hours after the level was supratherapeutic at 0.4 units/mL for a second time. At this new dosage, anti-Xa concentrations were recorded at 0.2 and 0.5 units/mL. The latter reading prompted a dose decrease of 14% to 12 mg (0.35 mg/kg) every 12 hours. The patient remained on this dosing regimen until enoxaparin was discontinued; anti-Xa concentrations were consistently in range at 0.2 and 0.3 units/mL.

Volume status changed frequently in this patient, offering a potential explanation as to why dosing requirements fluctuated throughout therapy. Hematological status varied dramatically, with hemoglobin and hematocrit levels as low as 3.7 g/dL and 11%, respectively. A total of 25 blood transfusions were required. Blood loss was deemed to have been a result of surgical interventions. Enoxaparin doses were held 12 hours prior to any surgical procedure in anticipation of blood loss; a total of 19 operations were performed. Therapy was re-started at the next regularly scheduled dose. Platelet levels fluctuated throughout therapy with no specific trend, the lowest being $68 \times 10^3/\mu\text{L}$. The patient was never tested for heparin-induced thrombocytopenia antibodies. Throughout the hospital stay, the patient's urine output fluctuated, requiring multiple doses of albumin and furosemide to increase urine output. When applying the Pediatric Modified Risk, Injury, Failure, Loss and End-stage criteria, the patient did meet criteria for injury, but not for renal failure. No empiric dose adjustments for enoxaparin were completed.

Patient 2. A 2-year-old, 13.2-kg Caucasian female presented with third-degree burns to 24% TBSA. Upon arrival, the patient was admitted to the general pediatric floor, and a PICC was placed in the patient's left femoral vein. VTE prophylaxis was initiated with 1 mg/kg (16 mg) of SC enoxaparin dosed once daily. After 2 doses, the dose was changed to 0.5 mg/kg (6.6 mg) SC every 12 hours. After 4 more doses, an anti-Xa level was obtained and documented at 0.21 units/mL. No dose adjustment

Table 1. Case Series of Pediatric Burn Patients Treated With IV Enoxaparin for VTE Prophylaxis

Case No.	Age, yr (Weight, kg)	TBSA (%)	VTE Risk Factors ^{12,13}	Enoxaparin Usage (Start Day-End Day)	Enoxaparin Dose/Route	Anti-Xa Level (units/mL)	Therapy Duration, Days (LOS, days)
1	10 (34)	75	Central line, mechanical ventilation, PICU admission, pneumonia, operations (25)	1–4	1 mg/kg every 24 hr (40 mg) SQ	0.5	145 (237)
				5–32	0.5 mg/kg every 12 hr (17 mg) IV	0.3, 0.2 (×3), 0.4 (×2)	
				33–50	0.41 mg/kg every 12 hr (14 mg) IV	0.2, 0.5	
				50–110	0.35 mg/kg every 12 hr (12 mg) IV	0.3, 0.2 (×4)	
				127–163	0.35 mg/kg every 12 hr (12 mg) IV	N/A	
2	2 (13.2)	24	Central line, operation (1)	1–2	1 mg/kg every 24 hr (16 mg) SC	N/A	12 (18)
				3–8	0.5 mg/kg every 12 hr (6.6 mg) SC	0.21	
				8–13	0.5 mg/kg every 12 hr (6.6 mg) IV	0.25	
3	8 (39.6)	8	Central line, operations (2)	1–2	1 mg/kg every 24 hr (40 mg) SC	N/A	12 (23)
				3–11	0.5 mg/kg every 12 hr (20 mg) IV	0.24, 0.45	
				11–13	0.35 mg/kg every 12 hr (14 mg) IV	N/A	

VTE, venous thromboembolism

was made, as the level was within the desired range. Three days later, for convenience and patient comfort purposes, the patient was transitioned from SC to IV enoxaparin at the same dose. After the third IV enoxaparin dose, an anti-Xa level was obtained and was documented at 0.25 units/mL. Anticoagulation therapy continued at the same dosage for the next 3 days and was discontinued after 12 total days of therapy.

The patient never required blood transfusions. Hemoglobin and hematocrit levels dropped as low as 7 g/dL and 21.4%, respectively. Throughout the hospital stay, the patient's renal function remained within normal limits.

Patient 3. An 8-year-old, 39.6-kg Caucasian female presented with second-degree burns to 8% TBSA. Upon arrival, the patient was admitted to the general pediatric floor, and a PICC was placed in the patient's right arm. VTE prophylaxis was initiated with 1 mg/kg (40 mg) of SC enoxaparin dosed once daily. The patient received 2 doses before being transitioned to the IV route at a dose of 0.5 mg/kg (20 mg) every 12 hours. After the third IV dose, an anti-Xa level was obtained and was documented at 0.24 units/mL. No dose adjustment was

made, as the level was within the desired range. Four days later, on hospital day 10, another anti-Xa level was obtained, which was found to be supratherapeutic at 0.45 units/mL. The dose was subsequently decreased by 30% to result in 0.35 mg/kg (14 mg) every 12 hours. However, no anti-Xa level was obtained after the dose adjustment. On the same day, the patient experienced a small nosebleed to the right nostril. Pressure and gauze were applied. The patient tolerated the interventions well, and the nosebleed stopped after approximately 15 minutes. Per the patient's mother, the patient had a past medical history of frequent nosebleeds prior to being on anticoagulation. Based on this history, no anti-Xa level was ordered, as the healthcare team did not believe the nosebleed to be related to enoxaparin therapy. The following day, the patient complained of pain near the PICC site. The PICC had no drainage, was non-erythematous, and was non-tender to palpation. An ultrasound was ordered, which ruled out a deep vein thrombosis in the right upper extremity. On hospital day 12, the PICC was removed, and enoxaparin therapy was discontinued at that time.

Table 2. Renal Function

Patient	SCr on Admission (mg/dL)	Highest SCr (mg/dL)	Lowest Urine Output (mL/kg/hr)	Pediatric Modified Risk, Injury, Failure, Loss and End-stage criteria Category
1	0.5	0.6	0.3	Injury
2	0.4	0.4	2.4	None
3	0.6	0.7	0.5	None

SCr, serum creatinine

Aside from the nosebleed described above, the patient did not experience any other bleeding episodes and did not require any blood transfusions. Hemoglobin and hematocrit were 9.8 g/dL and 27.3%, respectively, at the lowest point. The patient did experience a decrease in platelets of $\geq 50\%$, which occurred 3 days after enoxaparin was discontinued. The patient was never found to be thrombocytopenic. Although the patient was never tested for heparin-induced thrombocytopenia antibodies, enoxaparin therapy had already been discontinued by the time the drop-in platelets occurred.

Discussion

In this report, the details surrounding the use of IV enoxaparin in 3 pediatric burn patients were discussed. Patients were aged 2 to 10 years, and TBSA burns ranged from 8% to 75%. Central line access was a VTE risk factor in each of the cases, and all patients received SC enoxaparin before being transitioned to the IV route. Of the 16 anti-Xa concentrations obtained for the IV route, 12 were in range and 4 were supratherapeutic; no level was subtherapeutic. Doses of IV enoxaparin were initiated at 0.5 mg/kg every 12 hours, consistent with CHEST recommendations.⁴ The average IV total daily dose (0.35 to 0.5 mg/kg every 12 hours) required to achieve anti-Xa concentrations in the desired range (0.1–0.3 units/mL) correlated with the total daily dose for the SC route, suggesting that there may be no SC to IV dose conversion necessary. These findings are similar to the results from Diab et al,⁶ who reported that SC and IV enoxaparin had similar mean first anti-Xa concentrations, with the former reaching 0.22 units/mL and the latter reaching 0.17 units/mL ($p = 0.08$) when dosed prophylactically at 0.5 mg/kg twice daily in children aged 2 months and older. The study by Cies et al,³ however, had dissimilar findings.

When comparing the use of IV with SC enoxaparin for treatment purposes in pediatric cardiac ICU patients, the mean therapeutic IV dose was 1.31 mg/kg/dose, versus 0.9 mg/kg/dose for the SC route ($p = 0.016$). It is important to note, though, that the average weights were 5 kg and 31 kg for the IV and SC routes, respectively; this could potentially confound the results. Also of note, the average age for patients receiving IV enoxaparin was 2 years, versus 8 years for the SC route. As it is well established that infants require larger enoxaparin dosing requirements than do older

children, this most likely affected the results as well. The study by Ignjatovic et al⁷ had similar results; they observed that children up to 5 years of age required larger doses of SC enoxaparin than did children ≥ 6 years of age in terms of VTE treatment. With respect to the patients in our study, the oldest patient required the lowest enoxaparin dose (0.35 mg/kg), whereas the youngest patient required the highest dose (0.5 mg/kg/dose). These findings are in line with the previous studies and suggest that fixed dose administration of enoxaparin may be inappropriate.

Providing proper anticoagulation in pediatric burn patients is challenging for a variety of reasons. First, VTE risk factors remain less defined in pediatrics than they do in their adult counterparts.² Second, the burn injury itself imparts physiological changes that can affect the bioavailability of medications delivered via the extravascular route. Third, most enoxaparin dosing in pediatrics has been extrapolated from adult data.² In addition, there is no consensus on the range of anti-Xa concentrations for which to aim with prophylactic dosing, and no dosing algorithm exists at this time.

SC Enoxaparin in Pediatric Burn Patients. Although there are multiple studies and data that support enoxaparin dosing for VTE prophylaxis and treatment, as summarized by the CHEST guidelines, questions still remain on how the hypermetabolic state of burn patients affects medication dosing. McCormick et al⁸ suggest that the standard dosing set forth by CHEST provides inadequate anti-Xa concentrations. With respect to the pediatric population, Brown et al² prospectively evaluated 35 pediatric burn patients to determine if 0.5 mg/kg of SC enoxaparin, dosed twice daily, would result in anti-Xa concentrations between 0.2 and 0.4 units/mL. Initially, 21 (60%) patients had undetectable anti-Xa concentrations, and even after median dose adjustments of 25%, only 2 additional patients met the goal range. By the time enoxaparin was discontinued, a total of 18 (51%) patients failed to achieve a sufficient level of anticoagulation. The researchers reported that younger patients and those with a higher TBSA (%) burn were more likely to fall short of appropriate prophylactic concentrations. Another study by Ignjatovic et al⁷ had similar findings. This retrospective review of pediatric patients treated with SC enoxaparin found a twofold to threefold variation in individual dose requirements in children less than or equal to 5 years of age, with patients younger than 1 year necessitating the highest

Table 3. Hematological Status

Patient No.	Platelets, Admit ($\times 10^3/\mu\text{L}$)	Platelets, High ($\times 10^3/\mu\text{L}$)	Platelets, Low ($\times 10^3/\mu\text{L}$)	Platelets, Discharge ($\times 10^3/\mu\text{L}$)	Bleeding Events	No. of Blood Transfusions Required
1	286	588	68	510	All deemed due to surgical intervention	25
2	247	697	196	661	None	0
3	305	529	187	529	Nosebleed that lasted 15 min	0

doses and the greatest number of dosage adjustments. These studies suggest that a one-size-fits-all approach will not result in proper anticoagulation and that additional risk factors, other than the burn injury itself, along with patient intervariability, need to be considered. The use and validation of an enoxaparin dosing calculator in adults adds support to this notion, but no data to support its use in pediatrics exist at this time.⁹

IV Enoxaparin in Pediatric Patients. Data describing IV enoxaparin in children is even more limited. A literature search revealed 3 studies, each using enoxaparin for both treatment and prophylactic purposes. Cies et al³ retrospectively compared the use of a 30-minute enoxaparin infusion with the SC route in pediatric cardiac intensive care unit patients and found that pharmacodynamically the 2 routes were similar in reference to medication release characteristics and peak concentrations. This suggests an equal likelihood of achieving adequate anti-Xa concentrations with both routes of administration. The authors reported that weight-based dosing increased as the volume of distribution increased. In another retrospective study by Diab et al,⁶ IV enoxaparin achieved target anti-Xa concentrations faster than did the SC route in critically ill infants and children. The authors concluded that IV and SC enoxaparin were equally efficacious and that the former would be an attractive option to reduce patient distress. On the other hand, a third study by Cray et al¹⁰ reported on the use of IV enoxaparin in 7 PICU patients and observed larger anti-Xa concentrations at 1 to 2 hours post administration, rather than at the 4- to 6-hour mark recorded with the SC route. These concentrations were considerably reduced 6 to 8 hours after IV administration, suggesting pharmacokinetic differences compared with the SC route and the need for more frequent administration. However, the duration of the IV infusion was not provided, making interpretation of the results somewhat difficult.

Limitations. This report has several limitations. Being a case series, the sample size is very small ($n = 3$), thus limiting the generalizability of the results. Efficacy and safety information may also not have been fully documented in the electronic medical record system, and a retrospective study would be unable to account for any inconsistencies. Concern has also been raised¹¹

regarding variation among hospitals with respect to the reagents used for anti-Xa monitoring. In the span of this study, 2 different anti-Xa monitoring kits were used. However, neither kit contained exogenous anti-thrombin III, in theory conferring a more accurate indicator for the degree of anticoagulation.

Conclusions

To our knowledge, this is the first study describing the use of IV enoxaparin in pediatric burn patients. Preliminary results show that a 30-minute IV infusion of enoxaparin, initiated at a dose of 0.5 mg/kg every 12 hours, with dose adjustments as clinically indicated, may effectively be used to achieve adequate prophylactic anti-Xa peak concentrations (0.1–0.3 units/mL) in pediatric burn patients while potentially reducing patient distress. No adverse effects, major bleeding events, or treatment failures occurred. A prospective review is warranted to confirm these results and to identify any correlations between age, TBSA (%) burned, or the number of VTE risk factors present, as well as the dose of enoxaparin necessary to achieve sufficient anticoagulation in this patient population.

ARTICLE INFORMATION

Affiliations Department of Pharmacy (VNS, LKP), INTEGRIS Baptist Medical Center, Oklahoma City, OK

Correspondence Vonya N. Streetz, PharmD; vonya.streetz@integrisok.com

Disclosure The authors report no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Acknowledgments This research was presented in poster form at the 2017 American Society of Health-System Pharmacists (ASHP) Midyear meeting in Orlando, FL, on December 6, 2017. It was presented as a platform presentation at the Alcalde Southwest Leadership Conference in Houston, TX, on April 5, 2018, and at the Oklahoma Society of Health-System Pharmacists (OSHP) residency conference on May 21, 2018.

Accepted December 15, 2018

Copyright Published by the Pediatric Pharmacy Advocacy Group. All rights reserved.

For permissions, email: matthew.helms@ppag.org

REFERENCES

1. Meizoso J, Ray J, Proctor K, et al. Hypercoagulability and venous thromboembolism in burn patients. *Semin Thromb Hemost.* 2015;41(1):43–48.
2. Brown A, Faraklas I, Ghanem M, et al. Enoxaparin and antifactor Xa levels in pediatric acute burn patients. *J Burn Care Res.* 2013;34(6):628–632.
3. Cies J, Santos L, Chopra A. IV enoxaparin in pediatric and cardiac ICU patients. *Pediatr Crit Care Med.* 2014;15(2):e95–e103.
4. Monagle P, Chan A, Vesely S, et al. 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(suppl 2):e737S–e801S.
5. Multidisciplinary VTE Prophylaxis BEST Team, Cincinnati Children's Hospital Medical Center: Best Evidence Statement Venous Thromboembolism (VTE) Prophylaxis in Children and Adolescents. <http://www.cincinnatichildrens.org/service/j/anderson-center/evidence-based-care/bests/>, BEST 181. Accessed June 20, 2018.
6. Diab Y, Ramakrishnan K, Nath D, et al. IV versus subcutaneous enoxaparin in critically ill infants and children: comparison of dosing, anticoagulation quality, efficacy, and safety outcomes. *Pediatr Crit Care Med.* 2017;18(5):e207–e214.
7. Ignjatovic V, Najid S, Newall F, et al. Dosing and monitoring of enoxaparin (low molecular weight heparin) therapy in children. *Br J Haematol.* 2010;149(5):734–738.
8. McCormick E, Parbuoni K, Huynh D, et al. Evaluation of enoxaparin dosing and monitoring in pediatric patients at Children's Teaching Hospital. *J Pediatr Pharmacol Ther.* 2015;20(1):33–36.
9. Faraklas I, Ghanem M, Brown A, et al. Evaluation of an enoxaparin dosing calculator using burn size and weight. *J Burn Care Res.* 2013;34(6):621–627.
10. Crary S, Van Orden H, Journeycake J. Experience with intravenous enoxaparin in critically ill infants and children. *Pediatr Crit Care Med.* 2008;9(6):647–649.
11. Greene L, Law C, Raffini L, et al. Lack of anti-factor Xa assay standardization results in significant low molecular weight heparin (enoxaparin) dose variation in neonates and children. *J Thromb Haemost.* 2014;12(9):1554–1557.
12. Pannucci C, Osborne N, Park H, et al. Acquired inpatient risk factors for venous thromboembolism after thermal injury. *J Burn Care Res.* 2012;33(1):84–88.
13. Pannucci C, Osborne N, Wahl W. Creation and validation of a simple venous thromboembolism risk scoring tool for thermally injured patients: analysis of the National Burn Repository. *J Burn Care Res.* 2011;33(1):20–25.