Evaluation of anticoagulant monitoring in pediatric patients receiving enoxaparin for venous thrombosis treatment

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Abstract

Background A venous thromboembolism (VTE) is a blood clot that occurs secondary to vessel wall injury often from a central line insertion. Enoxaparin is often considered a first line treatment in pediatrics for VTE due to its favorable kinetic profile. Enoxaparin monitoring for pediatric patients is accomplished through anti-Xa monitoring although a correlation of efficacy and safety as yet to be established. The objective of this study is to evaluate covariates in pediatric patients to determine which variables are most likely to be associated with enoxaparin dose changes. Methods A single center, retrospective chart review was conducted in pediatric patients treated with enoxaparin for VTE over a 10-year period were assessed to determine covariates that lead to dose changes based off anti-Xa levels. Secondary outcomes described monitoring patterns at the University of New Mexico Children's Hospital. Results Sixty eight patients met inclusion criteria in which results showed that patients aged 2-5.9 months (p=0.026), critical care status (p=0.009), and of Native American ethnicity (p = 0.016) were likely to have an enoxaparin dose change at least once during their treatment regimen. The mean number of levels drawn were 7.5 per patient and doses were not frequently changed based off a confirmatory lab draw. However, many doses were adjusted based off the week 1 post therapeutic level. Conclusion In conclusion, we found that patients of Native American ethnicity, younger than 6 months, and those admitted to the pediatric intensive care unit were likely to have dose changes based on anti-Xa levels.

Introduction

A venous thromboembolism (VTE) is a blood clot that encompasses a deep vein thrombosis (DVT) or pulmonary embolism (PE), which leads to various signs, symptoms, and tissue destruction based on clot location. This usually occurs after injury to a vessel from central line insertion, trauma, surgery, and acute or chronic disease states that initiate the intrinsic or extrinsic coagulation cascade. Enoxaparin, a low molecular weight heparin, is considered the standard of care for VTE treatment in children due to greater predictability of kinetics and the ability to monitor levels.[1] It works by binding to and accelerating antithrombin III activity and therefore inhibiting coagulation factor Xa and IIa. Through Xa inhibition, the conversion of prothrombin to thrombin is inhibited, which leads to the prevention of a fibrin clot formation. Venous thromboembolism treatment varies based on many factors such as age, weight, renal function, and treatment indication.

According to CDC data from 1994 and 2009, 78,685 pediatric patients were discharged with a VTE diagnosis, of which 3740 were associated with an in-hospital death.[2] The annual incidence of VTE in children is 0.7 to 2.1 per 100,000 people and added an average cost of $25,000 per child per year.[3] These costs may include but are not limited to; length of stay, diagnostic tests, treatment, hospitalizations, outpatient visits, and comorbidity management.[4]

Enoxaparin therapeutic monitoring for pediatric patients is accomplished through anti-Xa monitoring with a goal of 0.5 to 1.0 IU/mL. At our institution, this level is usually drawn on average of 4 hours (3-6 hours)

after the second or third dose of a new dosing regimen. Traditionally in adult patients, anti-Xa monitoring is not routinely performed, mainly due to a potential of incorrectly drawing the levels and pharmacokinetic and pharmacodynamic stability in adult patients.[5-7] Monitoring may prove to be beneficial in adults if they have renal dysfunction or obesity. Studies have yet to demonstrate a true correlation between therapeutic levels and enoxaparin efficacy or safety, especially in children.[8-10] Hence, it is difficult to understand the full utility of monitoring of all children on enoxaparin therapy, which may lead to unnecessary health care costs.

The frequency of levels being drawn varies based on healthcare team's comfort level, especially when a therapeutic value is obtained. Currently, the only source that directs the number of times a level is drawn after a therapeutic level is based off of expert opinion, which is published in the 2012 CHEST guideline.[1,11] The recommendations are to check levels after starting a dose or dose change and once a correct dose is established based on the anti-Xa levels. It is then recommended to confirm using a repeat level, then check the following week and monthly once stable. The number of dose adjustments from the CHEST guideline initial dosing and dose adjustment guidelines have shown variability in adjustments in the pediatric population.[12] To our knowledge, a study has not yet evaluated the characteristics that are associated with enoxaparin dose changes in pediatric patients. The objective of this study is to evaluate covariates in pediatric patients to determine which variables are most likely to be associated with enoxaparin dose changes, which will lead to more predictable anticoagulant management.

Methods

Study population and data collection

A single center, retrospective chart review was conducted in which pediatric patients who met inclusion criteria that were treated with enoxaparin for VTE (including PE or DVT) over a 10-year period (2009-2019) were assessed. The study was approved by the Institutional Review Board at University of New Mexico Hospitals with waiver of informed consent. Patients were identified by ICD-9 or ICD-10 codes for VTE, PE, or DVT. Patients were included if they were 2 months to 18 years of age who had received an enoxaparin dose based on the CHEST guidelines for treatment of VTE and anti-Xa levels drawn to establish target attainment. Patients were excluded if they were neonates, on renal replacement therapy, prescribed enoxaparin for VTE prophylaxis, incomplete data for chart review, or patients who were not managed based on the CHEST guideline dosing recommendations. The primary objective of the study was to determine which characteristics led to enoxaparin dose changes in pediatric patients. The secondary objective was to determine the mean number of dosing changes needed to reach target level, the mean number of anti-Xa levels drawn, and explore the number of dose changes based on the confirmatory, week 1, and month 1 anti-Xa levels. See table 1 for variables analyzed.

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of New Mexico.[13] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Statistical analysis

All patients with an ICD-9 or ICD-10 codes for VTE, PE, or DVT were included in the analysis. The following demographic data were gathered for patients who met the inclusion criteria: age, sex, ethnicity, weight at enoxaparin initiation (if given, otherwise most recent weight, in kg), height (in cm), body mass index (BMI), serum creatinine at initiation of enoxaparin, and critical care status. The following anticoagulation data were gathered for patients meeting inclusion criteria: enoxaparin dose (mg/kg), anti-Xa levels, and number of enoxaparin dose changes. Data was analyzed using the statistical software, SPSS version 19.[14] The primary outcome was analyzed using a multiple logistic regression and secondary outcomes were reported through descriptive statistics.

Results

Patients

A total of 68 patient charts met inclusion criteria: patient demographics were summarized in Table 2. Of the 68 patients, 37 were male and 31 were female. Most patients were Hispanic followed by Caucasian then Native American at 50%, 34%, and 19%, respectively. Many of the patients were older than a year (74%), in which more than half of those were greater than 10 years (60%). One third of the patients were considered critical care status, defined as admittance to the pediatric intensive care unit at the start of enoxaparin. Only 7% of patients had acute kidney injury (AKI), defined as a creatinine increase by greater than 0.3 from baseline, more than 1.5-1.9 times the baseline value, or urine output less than 0.5 ml/kg/hr for 6-12 hours at the start of the first enoxaparin dose.[15]

Dose Changes

The primary outcome was to determine which characteristics led to enoxaparin dose changes in pediatric patients (Table 3). Results of the multiple logistic regression analysis showed that patients aged 2-5.9 months (p=0.026), critical care status (p=0.009), and of Native American ethnicity (p = 0.016) were likely to have an enoxaparin dose change at least once during their treatment regimen guided by anti-Xa levels. Characteristics generally thought to lead to dose changes such as age 6-11.9 months, AKI, and BMI $>$ 95 percentile were not statistically significant. These groups did have a smaller sample size, therefore potentially leading to an inability to find a significant correlation. Furthermore, the average starting dose of enoxaparin was 1.1 mg/kg/dose and the average number of dose changes were about 2 per patient (Table 4).

Anti-Xa levels

The secondary outcome sought to evaluate the number of dose changes based off anti-Xa confirmatory, week 1 and monthly levels, once a stable level was attained. Due to the retrospective nature of this study, not all anti-Xa levels were drawn consistently. A confirmatory, week 1, and monthly level were obtained in 45 and 52 patients correctly. Of these, 39/45 (87%) and 44/52 (85%) patients did not have a dose change based on confirmatory and monthly levels, respectively. A total of 33/52 (63%) of patients required a dose change based on the week 1 level. Additionally, the average number of levels drawn were 7.5 per patient, during a 6-12 week treatment period.

Discussion

In this retrospective study, we found that there were a few clinical characteristics that were correlated with an enoxaparin dosing change for VTE treatment. These characteristics included an age of 2-5.9 months, Native American ethnicity, and critical care status, which was defined as admittance to the pediatric intensive care unit at the start of enoxaparin. Interestingly, factors such as ages of 6-11.9 months, obesity, and AKI did not have statistical significance in terms of the likelihood of having dose changes after starting enoxaparin. Clinically, the non-statistical significance is potentially due to the low number of patients in our study. Over the 9-year period, there were only 68 patients who met inclusion criteria which is a fairly low number of patients treated for VTE, which indicates that the incidence of VTE is uncommon in children. Annually, it is estimated that the incidence of VTE in children is between 0.14 and 0.21 per 10,000 children.[16,17]

Secondary outcomes focused on enoxaparin monitoring practices. We found that pediatric patients on therapeutic enoxaparin received an average of 7.5 blood draws to check anti-Xa levels, but only received an average of 2 dose changes during a therapeutic course. In children who develop a VTE that has occurred with a clinical risk factor that has resolved, it is suggested to treat for 6-12 weeks.[1] Having 7.5 levels checked in that period of time is approximately one blood draw weekly to every other week. Many of these patients start their treatment in the hospital as it has been reported that the incidence of hospital acquired VTE is 30 episodes per 10,000 admissions.[18]Although costly, monitoring anti-Xa levels in the hospital is convenient. Once a patient is discharged, they must then return for blood draws, which is a painful procedure, therefore disrupting a normal routine and adding to the overall healthcare costs.

In the adult patient population, anti-Xa levels are not commonly checked, mainly due to more predictable pharmacokinetic variables, excluding obese and renal patients. One study examined 99 adult patients on treatment enoxaparin to determine if anti-Xa monitoring was necessary in the obese population.[19] It was noted that for safety and potential efficacy purposes, anti-Xa should be monitored in this patient population, although clinical outcomes related to anti-Xa monitoring are controversial. In a case series conducted by Ahuja et al, underweight and renally impaired adult patients were subtherapeutic with their first anti-Xa level and often required dose increases to achieve appropriate levels.[20] In these unique adult populations it is necessary to monitor levels while on enoxaparin treatment, but overall in general it is not considered standard of practice. By checking fewer levels, healthcare costs and patient inconvenience is decreased. Although we did not see a statistical significance for obesity or renal impairment leading to dose changes in our population, it is important to note that we strongly recommend continuing to check levels in these patients.

What also makes enoxaparin management difficult in the pediatric population is that dosing is not standardized as it is in adults. Doses are often started at 1 mg/kg twice a day but may vary based on age.[1] It is thought that infants up to 6 months require a higher weight based dose than other age groups, while infants 6 months to 12 months are slightly higher than children 1 year to 18 years all start at a standard dose. This variability drives the practice of checking anti-Xa often. Based on the results of our study, there is a possibility that we check levels too often in a population that does not necessarily require it. Standard practice has evolved to checking the first level before the second or third dose, a confirmatory level once stable, a one-week level then a one-month level and so on. Some practices may even check more often, which leads to higher healthcare costs and unnecessary blood draws.

Even with the results of our study, it is important to consider that some patients should still be monitored more frequently while on enoxaparin for safety and potential treatment efficacy. Included in this list are those that met the primary outcome such as critical care status, Native American ethnicity, and younger than 6 months of age. Although not detected in our analysis, we would recommend a conservative approach in frequent monitoring of patients under 10 years old, those with AKI, underweight, obese, or with a clinical judgment by the treating practitioner. That being said, in these sub-populations one could consider decreasing the number of tests drawn, one of which is the confirmatory test. Based on our results, it may be more cost effective and important to test after a week of a therapeutic level since it was found that 37% of our patients required a dose change after a week compared to 13% after the confirmatory level.

The first limitation to this study is the small sample size being evaluated and the lack of standardization of anti-Xa monitoring. If there was a larger sample, there may have been more data to recommend when to test versus not. Due to the infrequent VTE incidence in pediatrics, this could have been more adequate as a multicenter study. Secondly, this is a retrospective study, hence there are many individualized factors that could not be controlled. Although difficult to conduct, future multi-institutional prospective studies could provide beneficial information on dosing, monitoring, and treatment outcomes of enoxaparin use in the pediatric population. Lastly, the pediatric population is so variable with continuously changing kinetics and dynamics plus growth and development play an important role on how medications are dosed and monitored. Future studies should be focused on starting with a well-defined population that share similar characteristics. A focused approach can provide robust details that can eventually be expanded to the greater population.

Conclusions

In conclusion, we found that patients of Native American ethnicity, younger than 6 months, and those admitted to the pediatric intensive care unit were likely to have dose changes based on anti-Xa levels. Secondarily, it was noted that levels were potentially drawn too often without clinical benefit. An abundance of monitoring increases healthcare costs and is inconvenient for the patient without an essential clinical benefit. Although a level after the first week of a therapeutic enoxaparin dose may provide benefit, it is unclear if the confirmatory or monthly levels provide any clinical or safety benefit. Further prospective studies are warranted to better risk stratify which children require the multiple anti-Xa levels currently checked on all patients. We believe there is clinical equipoise to conduct a prospective study comparing

the methods of checking 2 levels (before the 3th dose and then at one week) versus checking our current standard 4 levels, which in the end becomes an average of 7.5 levels checked for 2 dose changes for a 6-12 week treatment course.

Conflict of Interest

The authors do not have any conflicts of interest to disclose

Data Sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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