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Enoxaparin Utilization Evaluation and Its Clinical and Laboratory Outcomes in Pediatric Patients in a Children's Teaching Hospital

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ABSTRACT

Background: In recent years, low molecular weight heparin use has increased in children. Dose of enoxaparin to achieve target anti-Xa and time to achieve anti-Xa are evolving and efficacy outcome data in terms of laboratory and clinical response rate in children still remains to be elucidated. Thus, in this drug utilization and evaluation study, we assessed patterns of enoxaparin use, its concordance with guidelines and laboratory and clinical outcomes in pediatric patients in a Children's teaching hospital.

Methods: In a prospective observational study, all pediatric patients with a thrombotic event who underwent treatment with enoxaparin were included. Demographic data, clinical outcome data based on follow-up sonography results, laboratory response based on anti-Xa and concordance with guidelines in terms of initial daily dose, duration of treatment, performing sonography to evaluate response, anti Xa check and time of anti-Xa check were evaluated.

Results: During a 9-month period, 41 pediatric patients suffered a thrombotic event and received enoxaparin. Median age of participants was 18.5 months. The anti-Xa level became therapeutic on mean day 4.7 with a mean enoxaparin dose of 1.24 mg/kg. Among participants 42% achieved therapeutic anti-Xa with initial empirical dosing. Less than 25 % of participants had a follow-up sonography and among them, 77% demonstrated complete thrombosis resolution after 4-6 weeks of enoxaparin therapy. We observed one major bleeding event. Concordance with guidelines was low in the aspects of duration of treatment, performing sonography to evaluate response and anti-Xa check.

Conclusion: With initial empiric dosing, it may take several days before anti-Xa become therapeutic. Among half of the children, a higher than recommended 1 mg/kg dose was required to achieve therapeutic anti-Xa level. Educational processes are mandatory regarding enoxaparin use and monitoring among clinicians to improve concordance with guidelines.

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Introduction

Enoxaparin in increasingly used in the pediatric population (1,2). This is due to increased rate of critically ill children and rate of thrombotic events (3, 4). According to CHEST guideline (5) monitoring anti-Xa is mandatory for children receiving low molecular weight heparins. However, there are still many questions regarding the best dose and timing to achieve therapeutic anti-Xa levels (1, 6). There are some studies that looked over low molecular weight heparins in children in regards to efficacy, time to achieve therapeutic anti-Xa with empirical dosing, appraising enoxaparin dose across age groups to achieve therapeutic anti-Xa, time to clot resolution, safety and

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other outcomes (1-3, 7-8). McCormick et al., assessed whether empirical enoxaparin doses would result in therapeutic anti-Xa concentrations, the median dose and time to therapeutic anti-Xa concentrations (1). The authors delineated that 37% of children achieved therapeutic level with empirical dosing, the therapeutic dose ranged from 1 to 1.9 mg/kg in children < 1-year-old and 0.6-1.5 mg/kg in those > 1 years old. Time to therapeutic anti-Xa was 5 days (median) (1).

Warad et al., evaluated outcomes of dalteparin use in children and illuminated an overall response rate of 83% defined by complete and partial thrombosis resolution (2). Bauman et al., assessed enoxaparin dosing requirements in children and depicted that higher starting doses would result in faster time to achieve target range (3). Schloemer et al., determined appropriate dosing in critically ill children receiving enoxaparin. They illustrated that younger children and those with worse illness severity require higher enoxaparin doses to achieve therapeutic anti-Xa. In the study, 42% of critically ill children and 29% of those receiving inotropes achieved therapeutic anti-Xa with empiric initial dosing. However, 81% achieved this outcome after dose titration (7).

Song et al., evaluated efficacy of enoxaparin in neonates in neonatal intensive care unit (NICU). They illuminated that 50% of neonates achieved clot resolution within 76 days of therapy and gender, clot location and postnatal age was associated with time to clot resolution (8).

However, to the authors' knowledge, there is no study evaluating laboratory and clinical response to enoxaparin and its concordance with guidelines in pediatric population in Iran. Thus, in this study we prospectively evaluated outcomes of enoxaparin use and concordance with guidelines to evaluate the pattern of enoxaparin prescription in a tertiary teaching hospital.

Methods

In an observational cross-sectional manner, this study was performed in intensive care units (ICUs) and general wards at the Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran and approved by Tehran University of Medical Sciences' Ethics Committee. In a prospective manner all hospitalized pediatric children aged below 18 years who had a thrombotic event and received enoxaparin were included in this study. Patients with clinically silent catheter related venous thromboembolism (VTE) and asymptomatic VTE were excluded from the study.

The primary outcome was to evaluate laboratory and clinical responses to enoxaparin by anti-Xa monitoring and follow-up sonography, respectively. The secondary outcome was to evaluate concordance of enoxaparin use and monitoring with guideline in terms of initial daily dose, duration of treatment, sonography performed or not to evaluate response, anti-Xa check, and time of anti Xa check.

After enrollment, demographic data of children including age, underlying condition, ward, indication of enoxaparin use (type of thrombosis), kidney and liver function were gathered. Underlying condition which was recorded included thrombophilia (protein S or C deficiency, nephrotic syndrome, malignancy, etc.). The reason for admission was also recorded. In another questionnaire enoxaparin use data was gathered including initial daily dose, time of administration, duration of therapy, clinical response assessed by sonography and laboratory monitoring. Follow-up sonography was anticipated 4-6 weeks after enoxaparin initiation or at the end of therapy duration. Clinical response was defined as new thrombosis, complete thrombosis resolution, partial thrombosis resolution, stable thrombosis, progression of thrombosis, progression to emboli formation, death and loss of limb/organ. Regarding laboratory monitoring therapeutic dose was defined as the dose that achieved target of peak anti-Xa 0.5-1 unit/ml. Additionally, time (in term of days) to therapeutic anti-Xa achievement was recorded.

Appropriate time to check anti-Xa was defined as level drawn between 4-6 hours after 3rd consecutive subcutaneous enoxaparin administration or dose change.

Anti-Xa of 0.5-1 unit/ml achievement was further classified as being a result of empirical dose or adjusted dose or fail to obtain. Empirical dose that was the initial recommended enoxaparin dosing was defined according to dose in the CHEST guideline in the treatment of thrombosis as enoxaparin dose of 1.5 mg/kg/dose q12 hours for infants below 2 months' age and 1 mg/kg/dose q12 hours for infants and children above 2 months' age. Accordingly, prophylaxis dose of enoxaparin for children under 2 months was defined as 0.75 mg/kg/dose q 12 hours, for children above 2 months 0.5 mg/kg/dose q 12 hours (4). Adjusted dose was defined as dosing that was adjusted based on the results of anti-Xa level to ultimately achieve target anti-Xa range (increased or decreased from 1 mg/kg). Adjustment of enoxaparin dose based on anti-Xa was performed according to nomogram (6,7). Fail to obtain anti-Xa level was defined as not reaching therapeutic anti-Xa of 0.5-1 unit/ml during treatment follow-up.

Appropriateness of treatment duration was assessed according to CHEST guideline and appropriate references (5,9).

Adverse effects including bleeding events and thrombocytopenia were recorded. Major bleeding was defined as bleeding requiring transfusion or hospital admission and bleeding into major organ/body cavity (2). Minor bleeding was defined as bleeding/bruising/oozing of injection and wound sites, small blood in urine /stool and minor epistaxis (2).

Analysis was done in IBM SPSS Statistics version 18. We have reported continuous variables as mean± SD. or median (IQR) and categorical variables are presented as a number (percentage). Normal distributional of continuous variables were assessed using kolmogorov-smirnov test.

Results

During 9-month study, 41 children had a thrombotic event and enoxaparin was initiated for them.

Median age was 18.5 months (1-184 months). There were 53% male. Median weight was 10.5 kg (2.5-40). 30% of participants were admitted to ICU, 26% were admitted in gastroenterology ward. 80% of participants had central venous catheter in line (CVC). None had hereditary thrombophilia. Types of thrombotic events and indications of enoxaparin is outlined in Table 1. Median duration of therapy was 32.5 days (6-120 days). No patient had impaired renal function.

Table 1. Types of thrombotic events and indications of enoxaparin.

Indications	N (%)
DVT Catheter-related	33 (80.5)
DVT Non- Catheter-related	2 (4.87)
Hepatic and portal vein thrombosis	2 (4.87)
Arterial ischemic stroke (without cardioembolic source)	1 (2.43)
Ulnar vein thrombosis	1 (2.43)
Arterial thrombosis	1 (2.43)
Prophylaxis of thrombosis	1 (2.43)

Clinical response was anticipated to be evaluated by sonography after 4-6 weeks of enoxaparin treatment. Among 41 participants, only 9 patients had sonography been performed at the time point. Among the 9 patients, 7 children had complete thrombosis resolution (77.7%). Table 2 depicts clinical response.

Table 2. Clinical response assessed by sonography.

Response	N (%)
New thrombosis	1 (11.1)
Complete thrombosis resolution	7 (77.7)
Stable thrombosis	0
Progression of thrombosis	0
Partial response	1 (11.1)
Progression to emboli formation	0
Loss of limb or organ	0
Death	0

Laboratory response was evaluated among 19 participants who had anti-Xa checked serially. Mean (±SD) time to achieve therapeutic anti-Xa was 4.7 (±3.6) days. Mean (±SD) therapeutic dose was 1.24 mg/kg (±0.35). Eight patients (8/19, 42.1%) had anti-Xa within the target range with empirical dosing, while nine (9/19, 47.3%) participants achieved therapeutic anti-Xa after dosing adjustment. Two patients failed to obtain a therapeutic anti-Xa level during study follow-up (2/19, 10.5%).

One patient developed major bleeding episode which was rectorrhagia. The patient had intractable seizure and a suspected metabolic disease. This patient received enoxaparin due to catheter related thrombosis. Anti Xa did not reach to therapeutic level in this patient. The patient received 18 days of enoxaparin and bleeding occurred at day 9. One patient developed minor bleeding (epistaxis).

Initial daily dose (starting dose) was 95% (39 out of 41 patients) in accordance with guideline. Two infants below 2 months of age did not receive the right initial dose.

Duration of treatment was only appropriate in 12% (5/41) of cases. Sonography to evaluate response was performed in 22% (9/41) of children.

Anti-Xa was checked in 46.3% (19 out of 41) of cases. Frequency of monitoring anti-Xa levels once therapeutic was only appropriate in 4.8% of participants (2 out of 41 patients). Anti-Xa collection time at peak level after the 3rd consecutive dose (steady state) was performed appropriately in all cases of whom anti-Xa was checked (19 out of 19 cases).

Discussion

In the present study, we evaluated patterns of enoxaparin use and its laboratory and clinical response in children. Results of this study illuminated that nearly half of the patients needed dose adjustment to achieve therapeutic level and anti-Xa become therapeutic after a mean of 4 days with average dose of 1.24 mg/kg. In addition, the results of this study illustrated that complete thrombosis resolution was achieved in the majority of cases after enoxaparin treatment; however, there is potential of bias due to low number of participants with a follow-up sonography. Finally, we observed that concordance with CHEST guideline was low in the aspects of duration of treatment, performing sonography to evaluate response and anti-Xa check.

It has been suggested that peak anti-Xa may be sub-therapeutic with current dosing recommendations (1). McCormick et al., evaluated enoxaparin dosing and monitoring in pediatric patients (1). Similar to our study, they observed 37% of patients achieved therapeutic anti-Xa with empirical dosing and concluded that there is a need for modification of empirical treatment of enoxaparin in children to ascertain therapeutic drug level in the majority of cases (1).

Warad et al., evaluated outcomes of dalteparin use in pediatric patients. The authors illustrated a favorable outcome of 83% overall response rate defined as complete and partial thrombus resolution (2). There were no progression or new thromboembolic events in the study. However, it should be noted that that in more than 75% of the patients in our study, clinical response could not be determined due to lacking sonography. Therefore, it seems that the response rate of 77% among 9 children with follow-up sonography could not be extrapolated to the whole study patients. Thus, regarding clinical response rate in our study, a firm comparison with Warad et al., cannot be made.

It has been demonstrated that critically ill children aged 61 days to 1 year or children who need inotrope support require higher doses of enoxaparin to achieve target anti-Xa level for the treatment of thromboembolic events. Schloemer et al., recommended starting dose of 1.3 mg/kg/dose every 12 hours in these children (7). In our study, while critically ill

children encompassed one third of the participants, mean therapeutic dose was 1.24 mg/kg. The best dosing strategy needs to be elucidated in further trials (7).

Song et al., evaluated efficacy of enoxaparin in neonates (8) in the NICU. The authors illuminated that 50% of neonates achieved thrombus resolution within 76 days of therapy. In the study the median dose and time to achieve therapeutic anti-factor Xa was 1.91 mg/kg and 6 days respectively. In addition, 25% of neonates had anti-Xa 0.5 to 1 unit/ml with initial recommended dosing (8). Importantly they elucidated that time to therapeutic anti-Xa attainment was not associated with time to clot resolution. Bleeding occurred in 9.3% of the neonates resulting in medication discontinuation.

Our results illuminated that the majority of children received the initial recommended doses of enoxaparin incorporated in CHEST guideline. However, the two infants below 2 months of age did not receive the right initial dose. Neonates and infants below 2 months of age require higher per kg doses of enoxaparin in comparison with older children and adolescents (5, 10, 11). Our results demonstrated that these age groups are at risk of underdosing. This emphasizes the need to be vigilant regarding dosing recommendations provided in the references.

This study had a number of limitations. First the low sample size of the participants. Second, poor concordance with guidelines made some outcome measures have potential bias. It is suggested to follow strict guidelines and written evidence-based protocols in hospital for LMWHs to conduct efficacy outcomes trials for LMWHs.

In conclusion, it may take several days before anti-Xa become therapeutic. Among half of the children a higher than recommended 1 mg/kg dose was required to achieve therapeutic anti-Xa level. Educational processes are mandatory regarding enoxaparin use and monitoring among clinicians to improve concordance with guidelines.

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