Neonatology

Brief Report

Neonatology 2021;118:345–347
DOI: 10.1159/000513784

Received: July 9, 2020
Accepted: December 11, 2020
Published online: March 18, 2021

Dalteparin in Newborn Thrombosis, Time for a New Starting Dose

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Keywords
Dalteparin · Low-molecular-weight heparin · Thrombosis · Dosing

Abstract
Background: Neonatal thrombosis is a frequently encountered complication in a neonatal intensive care unit. Dalteparin can be used to treat thrombosis in newborn infants. ***Objectives:*** In this study, we evaluate the current recommended starting dose of 129 ± 43 U/kg/24 h, hypothesizing that this dose is too low to reach therapeutic anti-Xa levels. ***Methods:*** From 2008 until 2017, all infants treated with dalteparin in the University Medical Centre Utrecht were included in this study. In this retrospective cohort study, the correlation between dose and anti-Xa level was observed. ***Results:*** Sixty-six infants were included. The most common thrombus types were catheter-related (29 patients, 44%) and venous sinus thrombosis (28 patients, 43%). The mean dalteparin dose needed for the first adequate anti-Xa level (0.5–1.0 IU/mL) was 297.6 U/kg/12 h. Two infants developed a first bleeding episode under dalteparin therapy; they both had anti-Xa levels in the therapeutic range. ***Conclusion:*** The increase of the starting dose of dalteparin will lead to earlier therapeutic levels of anti-Xa in the studied population and appears to be safe. However, this needs to be evaluated in further study.

Introduction

Neonatal thrombosis is a frequently encountered complication in a neonatal intensive care unit (NICU) with a reported incidence of 2.4–6.6 per 1,000 NICU admissions [1]. Risk factors for thrombosis in neonates are intravascular catheters, perinatal asphyxia, systemic infections, and pro-thrombotic factors [1–4]. Low-molecular-weight heparin (LMWH) is the therapy of choice. Doses are adjusted using anti-Xa level measurements, aiming at levels between 0.5 and 1.0 U/mL [5].

To the best of our knowledge, no data were reported on the use of dalteparin in preterm infants. It is well known that the infants' hemostatic system differs from that of adults, maturing until the age of 6 months [6]. The pharmacokinetics and pharmacodynamics of LMWHs are likely to differ from older children and adults, suggesting a higher dose for neonates and younger infants [7, 8]. This difference in coagulation physiology emphasizes the need to evaluate the efficacy of (starting) doses of LMWH in neonates of different gestational ages (GAs).

Materials and Methods

We report on a retrospective cohort study of all infants admitted to the NICU of the University Medical Center Utrecht between January 2010 and January 2017, who were treated with dalteparin,

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Table 1. Dose adjustment protocol for dalteparin based on anti-Xa levels (adopted from local protocol)

	Dose adjustment	Next anti-Xa sample
0.0–0.24, U/mL	Increase dose by 50%	After the second new dose
0.25–0.49, U/mL	Increase dose by 25%	After the second new dose
0.5–1.20, U/mL	No adjustment necessary	Weekly in the first month, then monthly
1.21–1.50, U/mL	Decrease dose by 25%	After the second new dose
>1.5, U/mL	Skip a dose then decrease dose by 50%	After the second new dose

Table 2. Dosing and response to treatment

Start dose, U/kg	185 (123–200)
Start anti-Xa level, U/mL	0.26 (0.18)
First effective dose, U/kg	289 (231–362)
First effective anti-Xa level, U/mL	0.60 (0.55–0.75)
Days until first effective dose, d	3.0 (1.0–5.0)
Dose at discharge, U/kg	315 (89)
Anti-Xa level at discharge, U/mL	0.63 (0.26)
Dose adjustments, *n*	3.0 (1.8)
Dalteparin treatment, *n*, d	73.0 (17.0–90.0)

Data are represented as mean with SD or median with IQR, where appropriate. IQR, interquartile range; SD, standard deviation.

the first-line treatment for thrombosis in our unit. We defined preterm birth as GA between 32 and 37 weeks, very preterm as GA between 28 and 32 weeks, and extreme preterm as GA less than 28 weeks. Subjects were identified by anti-Xa level measurements in the hospital laboratory for clinical chemistry and hematology. Since this was a retrospective study using anonymized patient information, approval by an ethical review board (METC, UMC Utrecht, 18-077C) was waived. We analyzed data for GA, sex, age at diagnosis, use of catheters, presence of infection at diagnosis, follow-up, and complications, mainly bleeding incidents. Anti-Xa levels, concerning the dose of dalteparin, were analyzed until resolution of the thrombus or the end of treatment. Statistical analysis was done using SPSS. Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using means and standard deviation in case of a normal distribution. Otherwise, medians and interquartile ranges (IQRs) were used. To compare doses between infants, we used the dose divided by the weight. The doses were administered twice daily, following local protocol.

Treatment was started when the thrombosis was symptomatic (persistent thrombocytopenia, signs of occlusion, hypertension), intracardial propagation, or occlusion of a major vessel was found. The local protocol advised a starting dose between 100 and 200 U/kg/dose twice daily administered subcutaneously (s.c.). This recommendation is based on the 2012 CHEST Guidelines for antithrombotic therapy in neonates [5]. Cranial ultrasound was performed routinely before initiation of treatment and then at least weekly until discharge. For venous sinus thrombosis, an MRI was performed for diagnosis and repeated before cessation of dalteparin therapy after 3 months. Routine blood samples for hemoglobin, thrombocytes, and electrolytes were part of routine clinical care during admission to the unit, and after discharge, they were sampled with the anti-Xa levels. If thrombocytopenia occurred, patients received thrombocyte transfusion according to local protocol.

Anti-Xa levels were measured (using the Liquid anti-Xa assay on the STA-R evolution coagulation analyzer [Diagnostica Stago, Asnieres-sur-Seine, France]) 4 h after administration, doses were adjusted according to the schedule from local protocol in Table 1. After initiation of therapy, the first sample was taken 4 h after the second dose. After every dose adjustment, a new anti-Xa level was measured after 2 new doses. With stable levels, weekly levels were measured in the first month, after that, monthly levels were taken.

Results

Sixty-six patients were included. Fifty-one infants were male (77%). Thirty-nine infants were born preterm (59%), of whom 27 (41%) very preterm, including 17 (26%) extremely preterm. The median birth weight was 2,231 g (IQR 975–3,238). The most common thrombus types were catheter-related (29 patients, 44%) and venous sinus thrombosis (28 patients, 43%). Most thrombi were venous of origin (49 patients, 74%), but also arterial (16 patients, 24%), and combined (1 patient, 2%).

In 47 (78.3%) of the cases, the initial response to treatment was shrinking of the thrombus. In 1 (1.7%) infant, the thrombus grew during treatment with dalteparin. In 12 (20.0%) cases, no direct change in thrombus size was observed.

The median dose at which the patient reached an anti-Xa level of 0.5 or higher for the first time was 289 U/kg/12 h (IQR 231–362). This was reached in a median of 3.0 days (IQR 1–5). The mean dose that led to an anti-Xa level between 0.5 and 1.0 was 327 U/kg/12 h.

The mean dose required to reach the first effective anti-Xa level was 303 U/kg/12 h (SD: 74) in premature infants as opposed to 296 (SD: 102) in term infants (p = 0.15). The very premature infants required a mean dose of 367 U/kg/12 h (SD: 100) (p = 0.71), and the extremely premature infants a mean dose of 313 U/kg/12 h (SD: 101) (p = 0.91).

Table 2 provides more dosing details and results. Twenty-two children had a history of bleeding before the start of LMWH. Of those patients, in 2 patients the bleeding restarted or increased while under treatment (bleeding in a nonrelated hemangioma, propagation of a preexisting intraventricular hemorrhage). The severity of the bleeding, according to the ISTH-criteria, was one instance of major bleeding and one instance of clinically relevant nonmajor bleeding. In one patient, the anti-Xa was 1.16, potentially explaining the bleeding.

In 2 patients, a first bleeding episode developed under LMWH treatment, again one instance of major bleeding and one instance of clinically relevant nonmajor bleeding (subcapsular hematoma of the kidney following a renal arterial thrombosis, upper leg hematoma). They both had anti-Xa levels in the therapeutic range.

Two patients died while under treatment, primarily due to the consequences of their thrombosis. Sixteen patients (25%) had lifelong sequelae of their thrombosis such as epilepsy, cognitive impairment, or chronic renal insufficiency, indicating the seriousness of their thrombotic events. Forty-five children (71%) had no persisting damage of their thrombosis. No other side effects from the treatment, such as thrombocytopenia, hyperkalemia, or elevated liver enzymes were found.

Discussion/Conclusion

Our results suggest the need for a higher starting dose of dalteparin in very ill neonates presenting with thrombosis. The mean effective dose (according to anti-Xa levels) in our cohort is 327 U/kg/12 h. We found a high interindividual variation in the first effective dose. The number of bleeding events seen in our study (4 cases of increased or initial bleeding) is similar to that seen in other studies in neonatal antithrombotic therapy [5]. Our cohort was possibly too small to identify differences between subgroups of different GA. According to our results, an initial dalteparin dose of 250–300 U/kg/12 h is suggested as a starting dose to reach adequate anti-Xa levels in these small children with further tailored treatment based on anti-XA levels. Evaluation of the efficacy (both regarding anti-Xa levels, thrombus clearance, and earlier on target) and safety (mainly bleeding) of our suggested approach in larger prospective cohort studies of (very) preterm infants is warranted.

Statement of Ethics

Since this was a retrospective study using anonymized patient information, approval by an ethical review board (METC, UMC Utrecht, 18-077C) was waived.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

F.S., D.V., A.H., and M.B. contributed to the design of the study, interpreted the data, drafted the work, and revised it for contend and made a final approval for submission. F.S. and D.V. were reasonable for the acquisition and analysis of the data.

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