

RESEARCH ARTICLE

Retrospective study evaluating safety, clinical effect, and dosing of dalteparin for the treatment of venous thromboembolism in term neonates

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Abstract

Background: There is an increased risk of venous thromboembolism (VTE) among neonates due to their unique hemostatic system. However, there is lack of approved treatment options for VTE in neonatal population. Importantly, dalteparin, a low molecular weight heparin approved for pediatric VTE in children ≥ 1 month of age, has also been used for the treatment of neonatal VTE. Based on the request from the Food and Drug Administration, this retrospective study aimed to characterize the safety, clinical effects, and dosing of dalteparin for treatment of VTE among neonates.

Procedure: Data from electronic medical records for neonates (born ≥ 35 weeks of gestation) treated with dalteparin for VTE between January 2010 and December 2021 were collected. The data assessed included bleeding and deterioration in hematological biomarkers among other adverse events, changes in relevant factor antifactor Xa (anti-Xa) levels and VTE status, and dosing of dalteparin and corresponding anti-Xa assay levels.

Results: Sixteen neonates from five participating sites in the United Kingdom were included. There were no bleeding events or deaths. Only one serious adverse event of hypoglycemic brain injury (unrelated to dalteparin) was documented in a patient with a history of hyperinsulinism. Median (range) daily dose of dalteparin at initiation was 309 (297–314) IU/kg. Eight of 16 neonates achieved therapeutic anti-Xa level, including two patients who did so after the first dose.

Conclusions: Dalteparin treatment in neonates raised no major safety concerns. Larger cohort studies may help provide further insights on clinical effects of dalteparin for neonatal VTE.

KEYWORDS

dalteparin, dosing, neonates, safety, venous thromboembolism

Abbreviations: AE, adverse event; anti-Xa, antifactor Xa; BID, twice daily; CT, computed tomography; CVC, central venous catheter; FDA, Food and Drug Administration; IU, international unit; LMWH, low molecular weight heparin; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

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1 | INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism (PE), is a major concern for morbidity and mortality.¹ In the pediatric population, the overall incidence of VTE is estimated to be 0.07–0.49 per 10,000.^{2–4} Importantly, VTE is an increasing complication in hospitalized pediatric patients, particularly those with central venous catheters (CVC), renal disease, congenital heart disease, neoplasm, inflammatory bowel disease, and other critical illnesses.² Hospital-acquired VTE among pediatric patients is estimated to be 30–58 events per 10,000 admissions.⁵ A case-control study conducted between January 2010 and March 2014 using the Children's Hospital Neonatal Database dataset reported that the incidence of VTE was 10.1 per 1000 admissions.⁶ Of note, studies have demonstrated an increased number of cases of VTE among neonates.^{7–9} A retrospective analysis in pediatric patients aged less than 2 years ($n = 346$) from 2011 to 2016 reported the majority of patients with VTE to be aged less than 0.5 years (78%), with neonates alone contributing 45% cases ($n = 156$) based on data collected from three countries (including North America, Europe, and Israel).¹⁰ The estimated incidence of VTE among neonates is reported to be 0.14–75 cases per 10,000 admissions.^{7,11–13} Neonates in particular are at greater risk of bleeding and other thrombotic complications due to their distinct developmental hemostatic system, which results in lower concentrations of coagulation factors and anticoagulant proteins.¹⁴ There is an increased risk of VTE among neonates with sepsis or those with indwelling CVC.¹²

Low molecular weight heparins (LMWHs) constitute the mainstay of anticoagulant therapy in pediatric patients. LMWHs bind to antithrombin to form a complex that irreversibly inactivates factor Xa, a key component involved in coagulation cascade and responsible for conversion of prothrombin to thrombin.¹⁵ Dosing of LMWHs is adjusted by monitoring antifactor Xa (anti-Xa) levels to achieve a defined therapeutic range (0.5–1 IU [international unit]/mL).¹²

Dalteparin (Fragmin), an LMWH, is the first anticoagulant therapy to be approved by the Food and Drug Administration (FDA) in May 2019 for the treatment of symptomatic VTE in pediatric patients aged ≥ 1 month.^{16,17} The FDA approval of dalteparin for the treatment of pediatric VTE was supported by the results of a phase II clinical study. This was a multicenter, open-label study that evaluated the safety, efficacy, and median dalteparin dose required to achieve therapeutic anti-Xa levels for acute VTE treatment in pediatric patients aged ≤ 18 years with and without cancer. In the study, VTE was resolved in 21/38 (62%) patients. Symptomatic recurrent VTE and clinically relevant bleeding were each reported in one patient within the cancer group (4%; $n = 26$) and no patients in non-cancer group (0%; $n = 12$), thereby demonstrating a consistent safety profile for dalteparin in pediatric patients.¹⁸

There is limited evidence supporting treatment of VTE in the neonatal population, and clinical practice is mostly extrapolated from recommendations and guidelines for adults and older pediatric patients.¹² Although not currently an approved therapy for neonates,¹⁶ dalteparin has been used in clinical practice for treating VTE during the

neonatal period (aged ≤ 28 days).^{9,19} Therefore, we conducted this non-interventional, retrospective study in response to a request from the FDA, which aimed to characterize the safety, effectiveness, and dosing of dalteparin treatment for VTE during the neonatal period (defined as ≤ 28 days old) in babies born ≥ 35 weeks of gestational age.

2 | METHODS

2.1 | Study design and setting

This descriptive, non-interventional cohort study utilized secondary data from electronic medical records on neonates treated with dalteparin for VTE. Data were collected from eligible patients admitted to neonatal intensive care units in the United Kingdom between January 2010 and December 2021. We characterized the safety profile of dalteparin by examining bleeding and deterioration in hematological biomarkers among other serious events, clinical effect of dalteparin by examining changes in relevant factor anti-Xa levels and VTE status, and dosing of dalteparin and corresponding anti-Xa assay levels. The study protocol was reviewed and approved by the Research Ethics Committee and Health Research Authority.

2.2 | Patient population and eligibility criteria

Neonates born at ≥ 35 weeks of gestational age at the time of initiation of dalteparin treatment for VTE (defined as thromboembolic events occurring in the venous circulation) and received one or higher dose of dalteparin were included in this study. Acceptable diagnostic modalities included compression ultrasound with Doppler, computed tomography (CT) with/without venography, magnetic resonance imaging with/without venography, conventional venography, conventional pulmonary angiogram, and ventilation-perfusion scan; spiral CT angiography was also permitted. Patients with bleeding disorders, including platelet dysfunction, disseminated intravascular coagulation, hemophilia, idiopathic thrombocytopenic purpura, or von Willebrand disease were excluded.

2.3 | Data collection and analysis

Data from electronic medical records of eligible patients were retrospectively collected from the date of initiation of dalteparin dosing, that is, the index date. Patients were then followed up until either of the following events occurred: 28 days after the last dose of dalteparin, death, loss to follow-up (defined as no follow-up visits documented in medical records post 28 days of the last dose of dalteparin), or end-of-study period (i.e., December 31, 2021). Data collected from the patient records included: patient demographic details (such as age at the time of first dose, sex, ethnicity, hospital admission and discharge dates, birth weight and at the time of dalteparin initiation); diagnostic details for VTE (method, date, and results); comorbidities and concomitant

medications; date and time of each dalteparin dosing; laboratory test results pre- and post-dalteparin treatment; and CVC at baseline and during the follow-up dose.

The safety, dosing, and effectiveness analysis set comprised patients who fulfilled all the inclusion criteria. Data collected for safety assessment included any bleeding events; deterioration in hematological biomarkers (platelets, hemoglobin, prothrombin time, and partial thromboplastin time); serious adverse events (AE) (defined as undesirable events resulting in death, or maybe life-threatening, require hospitalization, prolongation of hospitalization, or result in persistent or significant disability/incapacity); and death. Dosing details including timing and duration of dalteparin dose; dose interruption, discontinuation, or switching to another anticoagulant with respective dates and reasons; and indication and use of dalteparin (e.g., VTE). Similarly, the clinical effect of treatment was assessed based on (i) changes in anti-Xa levels (using the reference range 0.5–1 IU/mL), as documented in medical records, along with (ii) any statement in the medical record (physician note or radiology report conclusion) that the VTE had progressed, resolved, or undergone no change. All data were recorded in the electronic case report form and used for this analysis. The target sample size based on FDA recommendation was at least 12 neonates treated with dalteparin for VTE.

2.4 | Statistical analysis

Data were analyzed descriptively using SAS version 9.3 or higher. Mean, median, standard deviation (SD), first and third quartiles, minimum, and maximum values were reported for $n \geq 5$ for continuous and discrete variables. Imputation for missing values was not performed. The frequency and percentage of missing data were reported for each variable as applicable. Data values have been rounded per rules described previously.²⁰

3 | RESULTS

3.1 | Patient characteristics

A total of 18 neonates from seven sites in the United Kingdom were screened for entry into the study. Of these, 16 (89%) neonates were included from five participating sites. Two patients at other study sites failed to meet the inclusion criteria for age group and were excluded. Follow-up data were available for only 13 patients (81%) as three patients were lost to follow-up after discharge from hospital within 28 days of the last dose of dalteparin. Overall, the study population consisted of nine (56%) females and seven (44%) males, and patients were mostly White ($n = 13$, 81%; Table 1).

The majority of patients ($n = 15$; 93.8%) had one or more comorbid disease or non-drug allergy at the first dose of dalteparin, with sepsis being the most common ($n = 6$; 38%), followed by hyperinsulinism ($n = 3$; 19%). Concomitant medications (initiated prior to first dose of dalteparin) were reported for 12 (75%) patients (Table 1). Risk factors

TABLE 1 Patient demographics ($N = 16$).

Parameters	Results
Male, n (%)	7 (44)
Gestational age at birth (weeks), median (range)	39.3 (38.4–40.5)
Birth weight (kg), median (range)	2.6 (2.4–3.2)
Ethnicity, n (%)	
Not Hispanic or Latino	12 (75)
Not reported	2 (13)
Other	2 (13)
Race, n (%) ^a	
White	13 (81)
Black	1 (6.3)
Asian	1 (6.3)
Not reported	1 (6.3)
Other	1 (6.3)
Age at first dalteparin dose (days), median (range)	13.5 (11–19)
Weight on date of first dalteparin dose (kg), median (range)	3 (2.5–3.2)
Patients with ≥ 1 comorbidity or non-drug allergy, ^b n (%)	15 (93.8)
Comorbidity or non-drug allergy reported in ≥ 3 patients	
Sepsis	6 (38)
Hyperinsulinism	3 (19)
Patients with ≥ 1 concomitant medications, ^c n (%)	12 (75)
Concomitant medications reported in ≥ 5 patients	
Benzylpenicillin	6 (38)
Cefotaxime	7 (44)
Furosemide (furosemide)	7 (44)
Heparin	9 (56)
Morphine	6 (38)
Paracetamol	6 (38)
Vancomycin	5 (31)

Abbreviations: n , number of patients; N , total number of patients.

^aMultiple responses were allowed.

^bOngoing during the first dose of dalteparin.

^cInitiated prior to the first dose of dalteparin.

for VTE were reported in 10/16 (63%) patients; CVC ($n = 10$; 63%) and hospitalization ($n = 7$; 44%) were most common (Table S1). VTE was attributed to CVC in four patients (50%). Intubation was reported in nine patients (56%), all of which were for mechanical ventilation and none were related to VTE (Table S2).

3.2 | Safety

Only one serious AE, hypoglycemic brain injury was documented. This patient had a history of hyperinsulinism (onset before first dose of dalteparin). However, this AE was not related to dalteparin. No other

TABLE 2 Safety outcomes among neonates ($N = 16$) receiving dalteparin for the treatment of VTE.

Safety parameters	Patients, n (%)
Serious AE ^a	
Hypoglycemic brain injury (not related to dalteparin)	1 (6.3)
Bleeding events	0 (0)
Deaths	0 (0)

Abbreviations: AE, adverse event; n , number of patients; N , total number of patients; VTE, venous thromboembolism.

^aEvents were coded using MedDRA (Medical Dictionary for Regulatory Activities) version 25.0.

serious AEs, deaths, or other thrombotic events (such as thrombocytopenia) were documented. No patients experienced major bleeding or clinically relevant bleeding events during dalteparin treatment or follow-up (Table 2). Additionally, no noticeable differences were observed in laboratory test results 30 days pre- and post-dalteparin initiation (Table S3).

3.3 | Clinical effects of treatment

Overall, four out of 16 patients (25%) were documented to have resolved their VTE (Table 3). The treatment duration for three of four patients was 6 weeks and for the remaining one patient, it was 2 months.

3.4 | Dalteparin dosing

Overall, the mean duration of treatment for dalteparin was 62.44 ± 30.04 days. In one patient, the treatment was interrupted and restarted with a total of 52 days of treatment. Dalteparin was administered twice daily, in two divided doses; the median (range) total daily dose of dalteparin at initiation was 309 (297–314) IU/kg (Table 3). For all patients, the median (range) starting dose given twice daily (BID) was 154.5 (100–475) IU/kg, while the maintenance dose was 345 (96–723) IU/kg given BID (Table S4). Eight of the 16 patients achieved a target anti-Xa level (including the four patients with resolution of VTE); two of these achieved the target after the first dose of dalteparin, while the remaining six patients required one or more dose adjustments (data not shown). For the eight patients achieving target anti-Xa level, the median (range) starting dose given BID was 150.5 (100–310) IU/kg, while the maintenance dose was 347 (96–723) IU/kg (Table S4). All patients experienced a dose change for dalteparin, with a total of 82 changes in this study. The most common reason ($n = 15$, 93.8% patients) for dose change was not achieving therapeutic anti-Xa levels (Table 3). Results for anti-Xa tests associated with the first dose of dalteparin were documented for only five patients. The mean (\pm SD) anti-Xa levels of the first post-dose tests were 0.29 ± 0.19 IU/mL.

TABLE 3 Dalteparin dose and anti-Xa monitoring at baseline assessment ($N = 16$).

Parameters	Results
Daily dose of dalteparin at initiation (IU/kg), median (range)	309 (297–314)
Main reason for dalteparin dose change, n (%)	
Switch to another coagulant	1 (6.3)
VTE resolved	4 (25)
Other	16 (100)
For line insertion without coagulation problems	1 (6.3)
Prophylactic dose on discharge	1 (6.3)
Thrombus resolving	1 (6.3)
Unknown/missing	2 (13)
Anti-Xa level adjustment to achieve therapeutic level ^a	15 (93.8)
Treatment course completed	11 (69)
Anti-Xa monitoring at baseline assessment, median (range)	
First post-dose anti-Xa result (IU/mL), ^{a,b} median (range) $n = 5$	0.26 (0.17–0.30)
Additional post-dose anti-Xa result (IU/mL), ^c median (range) $n = 4$	0.44 (0.30–0.50)

Abbreviations: anti-Xa, antifactor Xa; n , number of patients; N , total number of patients; SD, standard deviation; VTE, venous thromboembolism.

^aStandard reference range for anti-Xa is 0.5–1.0 IU/mL.

^bResults for anti-Xa testing in association with the first dalteparin dose was available for 5 patients.

^c4/5 Patients had a combined total of 23 additional post-dose anti-Xa tests.

4 | DISCUSSION

This study presented findings on safety, clinical effect, and dosing from real-world data in 16 neonates treated with dalteparin for VTE. CVC and hospitalization were the most common risk factors for VTE. No bleeding events or deaths were documented. Four patients had documented evidence of resolution of VTE, and two patients achieved therapeutic anti-Xa levels at the first dose. The most common reason for dose change was to achieve therapeutic anti-Xa levels.

In this study, all patients had deep vein thrombosis (DVT) as their thromboembolic event; however, no cases of PE were reported. Notable differences exist in the etiology of VTE between neonates versus older pediatric patients and adults with respect to anatomical site, associated comorbidities, hemostatic physiology, and endothelial function.^{21,22} Although evidence regarding the incidence of PE among pediatric patients (including neonates) is very limited in the published literature or possibly underreported due to asymptomatic clinical manifestation,^{23,24} studies suggest PE as a rare occurrence in pediatric population compared to adults. A prospective, 2-year registry study from the Netherlands in pediatric patients with VTE reported PE

in one of 47 neonates (aged <1 month) versus nine of 52 older children (aged >1 month to ≤18 years).²⁵

In this study, the majority of the patients presented with a specific VTE risk factor, of which the most common were CVC and hospitalization. Other pediatric studies have also identified CVC as a predominant risk factor for VTE,^{3,9,10,25} which reportedly attributes to more than 90% of neonatal VTE cases.^{12,22} CVC placement constitutes a key factor for causing thrombosis leading to endothelial injury, followed by venous stasis, and is often associated with a hypercoagulable state based on Virchow's triad for VTE etiology.^{12,14} A case-control study from the United States in critically ill neonates admitted to the neonatal intensive care unit identified CVC as an independent risk factor for hospital-associated VTE. Other risk factors included hospitalization (≥15 days), mechanical ventilation, infection, and major surgery.¹¹ Our study did not statistically evaluate any risk factors and associated causality for etiology of VTE. Therefore, larger comparative studies adjusting for confounding factors would help to fully delineate the risk factors for neonatal VTE.

In the current study, one case of hypoglycemic brain injury, unrelated to dalteparin, was reported in a patient with a history of hyperinsulinism, which is reportedly a major cause for brain injury in neonates.²⁶ There were no documented safety concerns for dalteparin treatment in our study with respect to bleeding events, other thromboembolic events (such as thrombocytopenia), or deaths. A retrospective, cohort study reported two first bleeding episodes (one major and one clinically relevant non-major bleeding) out of 66 patients (gestational age <37 weeks) treated with dalteparin with median starting dose of 185 (123–200) IU/kg and treatment duration of 73 (17–90) days.⁹ Another study reported only two minor bleeding complications in each of the prophylactic ($n = 116$) and treatment ($n = 50$) groups for dalteparin among pediatric patients (aged ≤18 years). Importantly, no bleeding events noted in infants aged less than 1 year. Patients in therapeutic group with bleeding events were aged 11–18 years and treated with median dalteparin dose of 182.5 (43.1–357) IU/kg/day. While majority of patients had ≤3 months of treatment in the prophylactic group (104/116), it was mostly ≤6 months in the therapeutic group (41/50).²⁷ Taken together, these safety findings from neonates are consistent with the low risk of bleeding complications associated with the use of dalteparin as reported in older pediatric population.^{18,19,28}

In this study, a total of four patients had VTE resolved and eight patients achieved therapeutic anti-Xa levels. No evidence of recurrence or progression of VTE cases was documented during the follow-up, that is, up to 28 days following the last dose. These findings are further supported by the overall clinical profile of dalteparin and other LMWHs as reported for pediatric population,^{18,19,29} and provide insights about the effectiveness of dalteparin for the treatment of VTE in neonates in the absence of randomized clinical trials.

A high median daily starting dose of dalteparin, i.e., 309 (297–314) IU/kg based on real-world use for neonates was noted in our study. This is aligned with the pharmacokinetics and pharmacodynamics profile for LMWHs, which requires a higher dose in neonates compared to older pediatric patients and adults to reach therapeutic

anti-Xa levels (0.5–1 IU/mL).^{21,22} The total daily dose for dalteparin initiation in the two neonates who achieved the therapeutic target levels (at the first dalteparin dose) in our study were 300 IU/kg (data not shown). Importantly, the pharmacokinetic modeling analysis and simulation of dalteparin in pediatric patients by Damle et al. predicted that a starting dose of 200 IU/kg would achieve a therapeutic anti-Xa level in 50% of infants from 0 to less than 8 weeks of age. However, the youngest patient with data in that study was 1 month old, and the authors suggested additional data are needed for neonates ≤1 month of age.³⁰ This is in contrast with the age limit of neonatal population used in our study (≤28 days), which may have attributed to the slightly higher starting dose documented in this study. Currently, dalteparin dosing data for neonates aged ≤28 days are very limited. The retrospective cohort study by Steenman et al. reported a higher mean (\pm SD) dose of dalteparin in preterm infants compared to term infants (303 ± 74 vs. 296 ± 102 IU/kg/12 h).⁹ Nevertheless, it is recommended to closely monitor the starting dose for dalteparin in the neonate population. Further studies providing better clinical correlation may be useful to understand and establish the starting dose for dalteparin among neonates.

Given the current lack of approved anticoagulant therapy and limited evidence on management of VTE in the neonatal population, the findings of this study are particularly relevant for informing clinical practice on the use of dalteparin for treatment of VTE in this population. Additionally, the real-world findings presented in this study may help to address the significant knowledge gap, and supplement the limited clinical evidence associated with neonatal VTE and the corresponding dalteparin dosing. The major limitations of this study include a small sample size and variability in patient characteristics and hence, the findings must be interpreted with caution. This study was based on a small cohort of neonates in the United Kingdom ($n = 16$), which may limit generalizability of findings. Data for anti-Xa level were available for eight out of 16 patients, and so it was only possible to confirm the anti-Xa target ranges for these eight patients. Furthermore, the retrospective observational design of this study based on the available real-world data retrieved from the electronic medical records of patients does not allow evaluation of causal relationships and may increase the likelihood of missing data or incomplete data. Of note, the study did not assess any formal hypothesis for safety, effectiveness, or dosing recommendations of dalteparin use for the treatment of VTE in neonates. Different centers may have varying expertise and treatment protocols, which may have led to differences in patient management across participating sites.

5 | CONCLUSIONS

This retrospective study did not identify any safety concerns including major and minor bleeding events with the use of dalteparin for the treatment of VTE in neonates. The small sample size limited the ability of the study to assess the effectiveness of dalteparin. Nevertheless, safety and clinical effects of dalteparin for the treatment of VTE in neonates observed in this study are consistent with other pediatric

studies. Considering that there are differences in the starting doses between neonates and older pediatric patients, larger prospective cohort studies may be warranted to guide the clinical use of dalteparin for appropriate management of neonatal VTE.

AUTHOR CONTRIBUTIONS

Nancy Sherman and Kevin Wolter: Conceptualization. **Nancy Sherman and Muhammad Younus:** Investigation; supervision. **Nancy Sherman, Muhammad Younus, Kevin Wolter, and Elaine M. Boyle:** Methodology. **Nancy Sherman:** Formal analysis. **Nancy Sherman, Suresh Victor, Venkatesh Kairamkonda, and Elaine M. Boyle:** Resources. **Suresh Victor, Venkatesh Kairamkonda, and Helen Brotherton:** Data curation. **Nancy Sherman:** Visualization; Writing original draft. **YM:** Project administration and funding acquisition; All authors: Writing-critical review and editing, approval of final version of this manuscript.

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CONFLICT OF INTEREST STATEMENT

Nancy Sherman, Muhammad Younus, and Kevin Wolter are Pfizer employees and may hold stock options with Pfizer. Suresh Victor, Venkatesh Kairamkonda, Eleri Adams, Helen Brotherton, and Elaine M. Boyle do not have any conflicts of interest relevant to this study.

DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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REFERENCES

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med*. 2010;38(Suppl 4):S495-S501. doi:10.1016/j.amepre.2009.12.017
2. Mahajerin A, Croteau SE. Epidemiology and risk assessment of pediatric venous thromboembolism. *Front Pediatr*. 2017;5:68. doi:10.3389/fped.2017.00068
3. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. *Blood*. 1994;83(5):1251-1257.
4. Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. *J Pediatr*. 2004;145(4):563-565. doi:10.1016/j.jpeds.2004.06.021
5. Witmer CM, Takemoto CM. Pediatric hospital acquired venous thromboembolism. *Front Pediatr*. 2017;5:198. doi:10.3389/fped.2017.00198
6. Bhat R, Kumar R, Kwon S, Murthy K, Liem RI. Risk factors for neonatal venous and arterial thromboembolism in the neonatal intensive care unit—a case control study. *J Pediatr*. 2018;195:28-32. doi:10.1016/j.jpeds.2017.12.015
7. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics*. 2009;124(4):1001-1008. doi:10.1542/peds.2009-0768
8. Demirel N, Aydin M, Zenciroglu A, et al. Neonatal thrombo-embolism: risk factors, clinical features and outcome. *Ann Trop Paediatr*. 2009;29(4):271-279. doi:10.1179/027249309X12547917868961
9. Steenman F, Vijlbrief DC, Huisman A, Bierings M. Dalteparin in newborn thrombosis, time for a new starting dose. *Neonatology*. 2021;118(3):345-347. doi:10.1159/000513784
10. Chan A, Lensing AWA, Kubitz D, et al. Clinical presentation and therapeutic management of venous thrombosis in young children: a retrospective analysis. *Thromb J*. 2018;16:29. doi:10.1186/s12959-018-0182-4
11. Amankwah EK, Atchison CM, Arlikar S, et al. Risk factors for hospital-associated venous thromboembolism in the neonatal intensive care unit. *Thromb Res*. 2014;134(2):305-309. doi:10.1016/j.thromres.2014.05.036
12. Fort P, Beg K, Betensky M, Kiskaddon A, Goldenberg NA. Venous thromboembolism in premature neonates. *Semin Thromb Hemost*. 2022;48(4):422-433. doi:10.1055/s-0041-1740267
13. van Elteren HA, Veldt HS, Te Pas AB, et al. Management and outcome in 32 neonates with thrombotic events. *Int J Pediatr*. 2011;2011:1. doi:10.1155/2011/217564
14. Witmer C, Raffini L. Treatment of venous thromboembolism in pediatric patients. *Blood*. 2020;135(5):335-343. doi:10.1182/blood.2019001847
15. Spronk HM, de Jong AM, Crijns HJ, Schotten U, Van Gelder IC, Ten Cate H. Pleiotropic effects of factor Xa and thrombin: what to expect from novel anticoagulants. *Cardiovasc Res*. 2014;101(3):344-351. doi:10.1093/cvr/cvt343
16. Merino M, Richardson N, Reaman G, et al. FDA approval summary: dalteparin for the treatment of symptomatic venous thromboembolism in pediatric patients. *Pediatr Blood Cancer*. 2020;67(12):e28688. doi:10.1002/pbc.28688
17. FRAGMIN (dalteparin sodium) injection. Pfizer. Accessed February 15, 2024. <https://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=2293>
18. Hartman LR, Nurmeev I, Svirin P, et al. A phase 2 pharmacodynamic dose-finding, safety, and efficacy study of dalteparin for pediatric venous thromboembolism treatment in children with and without cancer. *Pediatr Blood Cancer*. 2022;69(8):e29764. doi:10.1002/pbc.29764
19. O'Brien SH, Kulkarni R, Wallace A, Hamblin F, Burr S, Goldenberg NA. Multicenter dose-finding and efficacy and safety outcomes in neonates and children treated with dalteparin for acute venous thromboembolism. *J Thromb Haemost*. 2014;12(11):1822-1825. doi:10.1111/jth.12716
20. Cole TJ. Too many digits: the presentation of numerical data. *Arch Dis Child*. 2015;100(7):608-609. doi:10.1136/archdischild-2014-307149
21. Haley KM. Neonatal venous thromboembolism. *Front Pediatr*. 2017;5:136. doi:10.3389/fped.2017.00136
22. Monagle P, Newall F. Management of thrombosis in children and neonates: practical use of anticoagulants in children. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):399-404. doi:10.1182/asheducation-2018.1.399
23. Navanandan N, Stein J, Mistry RD. Pulmonary embolism in children. *Pediatr Emerg Care*. 2019;35(2):143-151. doi:10.1097/pec.0000000000001730

24. Dijk FN, Curtin J, Lord D, Fitzgerald DA. Pulmonary embolism in children. *Paediatr Respir Rev*. 2012;13(2):112-122. doi:[10.1016/j.prrv.2011.09.002](https://doi.org/10.1016/j.prrv.2011.09.002)
25. van Ommen CH, Heijboer H, Büller HR, Hirasig RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in the Netherlands. *J Pediatr*. 2001;139(5):676-681. doi:[10.1067/mpd.2001.118192](https://doi.org/10.1067/mpd.2001.118192)
26. Chandran S, Samuel Rajadurai V, Alim Abdul Haium A, Hussain K. Current perspectives on neonatal hypoglycemia, its management, and cerebral injury risk. *Res Rep Neonatol*. 2015;5:17-30. doi:[10.2147/RRN.S55353](https://doi.org/10.2147/RRN.S55353)
27. Warad D, Rao AN, Mullikin T, et al. A retrospective analysis of outcomes of dalteparin use in pediatric patients: a single institution experience. *Thromb Res*. 2015;136(2):229-233. doi:[10.1016/j.thromres.2015.05.017](https://doi.org/10.1016/j.thromres.2015.05.017)
28. Nohe N, Flemmer A, Rümmler R, Praun M, Auberger K. The low molecular weight heparin dalteparin for prophylaxis and therapy of thrombosis in childhood: a report on 48 cases. *Eur J Pediatr*. 1999;158(3):S134-S139. doi:[10.1007/pl00014339](https://doi.org/10.1007/pl00014339)
29. Dix D, Andrew M, Marzinotto V, et al. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr*. 2000;136(4):439-445. doi:[10.1016/s0022-3476\(00\)90005-2](https://doi.org/10.1016/s0022-3476(00)90005-2)
30. Damle B, Jen F, Sherman N, Jani D, Sweeney K. Population pharmacokinetic analysis of dalteparin in pediatric patients with venous thromboembolism. *J Clin Pharmacol*. 2021;61(2):172-180. doi:[10.1002/jcph.1716](https://doi.org/10.1002/jcph.1716)

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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