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Original Research

Systematic review and meta-analysis of individualized enoxaparin dose optimization in critically ill pediatrics: A path towards enhanced therapeutic outcomes

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Abstract

Background: Critically ill pediatric patients face an increased risk of venous thromboembolism, and enoxaparin is commonly used for prophylaxis and treatment. However, optimal dosing in this population remains uncertain, and individualized dose optimization is seen as a promising approach. This systematic review aims to refine dosing strategies in critically ill pediatric patients, with the goal of improving outcomes and reducing VTE and bleeding complications. **Methods:** The study followed PRISMA guidelines and employed a comprehensive search strategy using relevant MeSH terms and keywords. Data extraction and management were performed using standardized protocols. The quality of the included studies was assessed using appropriate tools. The statistical analysis was performed using R software (Version 4.3.0, Vienna, Austria) and RStudio interface (Version 2023.03.0, Boston, MA, USA). **Results:** The systematic review included 15 studies on individualized dosing strategies of enoxaparin in critically ill pediatric patients. The studies revealed variations in dosing strategies, including higher initial doses for neonates and infants. The administration route (IV or SC) and dosing frequency were also explored, with some studies suggesting IV administration as an alternative to SC. Clinical outcomes such as time to therapeutic anti-Xa levels, bleeding events, side effects, and the development of venous thromboembolism were assessed. Anti-Xa level-directed dosing and weight-based dosing were found to yield optimal outcomes. Meta-analysis results showed low mortality rates, a low incidence of thrombotic events with therapeutic prophylactic doses, and a low frequency of bleeding events. **Conclusion:** This systematic review concluded that initial high dose of enoxaparin is required to achieve therapeutic levels. However, limited data regarding dose optimization of enoxaparin is available on critically ill pediatrics. Pharmacokinetic studies, therapeutic drug monitoring, and population pharmacokinetic modelling can guide personalized dosing decisions. The implementation of personalized dosing protocols in clinical practice has the potential to improve patient care, enhance safety, and optimize anticoagulation management in critically ill pediatrics. Further research including prospective studies and RCTs is essential to establish pediatric-specific dosing guidelines and target anti-factor Xa ranges for enoxaparin in critically ill pediatrics.

Keywords: systematic review; meta-analysis; enoxaparin; dose optimization; pediatrics; therapeutic outcome

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INTRODUCTION

Critically ill pediatric patients often face a multitude of challenges, including increased risk of thromboembolic events due to their underlying conditions and the necessary medical interventions they receive.[1] Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, poses a significant threat to the well-being and recovery of these vulnerable patients.[2] Enoxaparin, a low molecular weight heparin, is commonly used for prophylaxis and treatment of VTE in the pediatric population.[3] However, the optimal dosing of enoxaparin in critically ill children remains a complex and evolving area of research.[4,5] Individualized enoxaparin dose optimization represents a promising approach to enhance therapeutic outcomes and minimize adverse events in critically ill pediatric patients.[6]

Enoxaparin has been extensively studied in adults, leading to established dosing guidelines based on body weight, age, and renal function. However, applying these guidelines to critically ill pediatric patients is challenging due to physiological differences, significant variability in drug response, and the limited evidence specific to this population.[7,8] The need for individualized dosing strategies has become increasingly evident, as standardized dosing regimens may lead to suboptimal therapeutic outcomes or an increased risk of bleeding complications.[6,9] The concept of individualized enoxaparin dose optimization involves tailoring the dose to a patient's specific characteristics, such as body weight, age, organ function, and other relevant factors.[6] The goal is to achieve therapeutic anticoagulation while minimizing the risk of bleeding. Personalized medicine approaches, including pharmacokinetic and pharmacodynamic modeling, as well as bedside monitoring techniques, offer promising avenues for optimizing enoxaparin dosing in critically ill pediatric patients.[8] Moreover, advancements in technology and the availability of bedside monitoring techniques, such as anti-factor Xa levels, have facilitated the evaluation of enoxaparin's effectiveness and the identification of patients who may benefit from dose adjustment.[10] Real-time monitoring allows clinicians to assess drug exposure and anticoagulant effect, enabling them to make informed decisions regarding dosage adjustments to achieve optimal outcomes.[11]

In recent years, there has been a growing body of research focusing on individualized enoxaparin dose optimization in critically ill pediatric populations. Several studies have investigated the impact of factors such as age, body weight, coagulation parameters, and renal function on enoxaparin pharmacokinetics and pharmacodynamics. These investigations have revealed substantial inter-individual variability, underscoring the need for tailored dosing strategies. Therefore, this systematic review and meta-analysis was crucial to refine enoxaparin dosing strategies in critically ill pediatric patients, ultimately improving patient outcomes and reducing the burden of VTE and bleeding complications.

MATERIALS AND METHODS

Research Question and Study Protocol

In order to investigate the individualized enoxaparin dose optimization in critically ill pediatric patients, a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted.[12] A study protocol was developed, which included the objectives, inclusion and exclusion criteria, search strategy, data extraction plan, and analysis methods.

Search Strategy

The search strategy was a crucial step in conducting this systematic review and meta-analysis. It involved designing a comprehensive and systematic approach to identify relevant studies from various sources. The search was limited to studies published in English.

Identification of Databases

Select relevant electronic databases that cover the biomedical literature including PubMed/MEDLINE, Embase, Google Scholar and Cochrane Library were searched.

Selection of Medical Subject Headings (MeSH) Terms and Keywords

A list of MeSH terms and relevant terms and keywords that accurately represent the key concepts of the research question including "enoxaparin," "pediatrics," "critically ill," "individualized dosing," "pharmacokinetics," and "pharmacodynamics." was developed.

Boolean Operators and Truncation

Boolean operators (such as "AND," "OR," and "NOT") to combine search terms and refine search results were also utilized. For example, combining "enoxaparin" AND "pediatrics" AND "individualized dosing" narrow down the search to articles that include all of these terms.Truncate terms when necessary to capture different variations of a word like using "pediat*" retrieved results containing "pediatric" and "pediatrics."

Search Syntax

The search syntax using the selected MeSH terms, keywords, and Boolean operators were constructed like (enoxaparin OR low molecular weight heparin) AND pediat* AND (individualized dosing OR personalized dosing) AND (critically ill OR intensive care OR ICU)

Manual Search

Manual searches by reviewing the reference lists of relevant articles, systematic reviews, and meta-analyses to identify additional studies that may have been missed in the electronic database search were conducted. Citation tracking by checking the articles that have cited the included studies to identify potentially relevant publications was also performed.

Data Management

Reference management software (EndNote 20) to organize and manage the retrieved citations and eliminate duplicate records was used.

Inclusion and Exclusion Criteria

Both randomized controlled trials (RCTs) and non-randomized studies (observational studies, cohort studies, case-control studies) were included. Critically ill pediatric patients (aged 0-18 years) receiving enoxaparin therapy for prophylaxis or treatment of venous thromboembolism (VTE) were included. Studies that assess individualized enoxaparin dose optimization strategies, including adjustments based on patient-specific factors such as body weight, age, renal function, and other relevant parameters including comparing individualized enoxaparin dosing strategies with standard fixed-dose enoxaparin regimens or other alternative dosing approaches were evaluated.

Exclusion Criteria

Animal studies, in vitro studies, reviews, case reports, editorials, and conference abstracts were excluded. Studies with insufficient data or incomplete reporting, making it impossible to extract relevant information or studies not published in the English language were also not included in final synthesis. Studies that focus exclusively on adult populations or non-critically ill pediatric populations were also excluded.

Study Selection

Two independent reviewers screened the titles and abstracts of the retrieved articles to assess their eligibility based on predefined inclusion and exclusion criteria. Full-text articles were obtained for potentially eligible studies, and the same reviewers independently assessed them for final inclusion. Any disagreements were resolved through discussion or consultation with a third reviewer.

Data Extraction

Data from the included studies were extracted using a standardized data extraction form. The following information was collected: study characteristics (authors, year of publication, study design and duration, location), sample size, patient characteristics, interventions (enoxaparin dosing strategies including initial and therapeutic dosing), outcomes (efficacy, safety, bleeding complications), and other relevant data. Any discrepancies in data extraction were resolved through consensus or by involving a third reviewer.

Quality Assessment

The quality of the included studies was assessed using appropriate tools, such as the Newcastle-Ottawa Scale (for non-randomized studies) or the Cochrane Risk of Bias Tool (for randomized controlled trials). Each study was independently evaluated by two reviewers, and any disagreements were resolved through discussion or by involving a third reviewer.

Data Synthesis and Analysis

The statistical analysis was performed using R software (Version 4.3.0, Vienna, Austria) and RStudio interface (Version 2023.03.0, Boston, MA, USA). The function Metaprop was utilized to estimate the proportion of adverse events using the reported number of events and the total number of patients. The statistical heterogeneity between the studies were assessed using chi-square test, I2 index statistics visual inspection of forest plots. The heterogeneity was considered significant when I2 value was greater than 50%.

Interpretation and Reporting of Results

The findings of the systematic review and meta-analysis were interpreted in light of the research question and the quality and heterogeneity of the included studies. Implications for clinical practice and future research were considered. The systematic review and meta-analysis were reported according to the PRISMA guidelines. A comprehensive and transparent report was prepared, including a flow diagram illustrating the study selection process, a detailed description of the included studies, the results of the meta-analysis, and a discussion of the findings.

RESULTS

The PRISMA 2020 flow diagram for the systematic review that included searches of databases is shown in figure 1. In first stage, the search strategy identified 884 potentially relevant records from various databases based on search strategy. The next stage involved removing any duplicate records identified from the initial search (n=321) and records marked as ineligible by automation tools (n=156), and records removed for other reasons (n=214). At the records screening stage, the 193 records were screened based on their titles and abstracts to identify potentially relevant studies. Out of these, 67 records were excluded at this stage based on the inclusion/exclusion criteria of the systematic review. The remaining 126 records were obtained in full-text format for further assessment of eligibility. Out of these, 51 records were not retrieved due to various reasons such as unavailability or access restrictions. The 75 retrieved records were assessed for eligibility based on the inclusion/exclusion criteria of the systematic review. Finally, a total of 15 studies were included in the systematic review, which met the inclusion/exclusion criteria and were relevant to the research question. Table 1 provides a comparison of different studies on the dosing strategy of enoxaparin in critically ill pediatrics. (figure 2)

Dosing Strategies

The dosing strategies for enoxaparin in critically ill pediatrics varied across the studies included in this systematic review. Different approaches were observed for both treatment and prophylaxis, involving variations in dose, route of administration (intravenous [IV] or subcutaneous [SC]), and dosing frequency. Some studies recommended higher initial doses of enoxaparin than those suggested by guidelines, particularly for neonates and infants, as the guideline-recommended doses were found to be inadequate in achieving therapeutic levels.[13,14] The safety and efficacy of IV and SC administration of enoxaparin were compared in several studies. Diab et al. (2017) found that IV infusion over 30 minutes was safe and equivalent to SC dosing in critically ill pediatric patients. Cies et al. (2014) reported that a 30-minute IV infusion produced therapeutic 4-hour anti-Xa levels similar to SC dosing. These findings suggest that IV

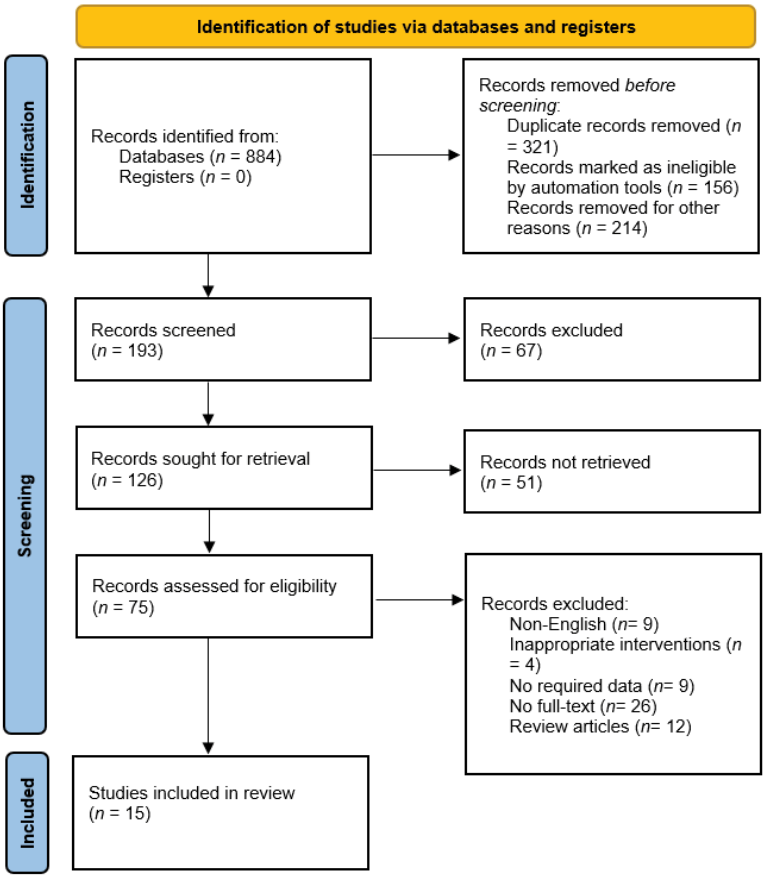

Figure 1. Flowchart of included studies

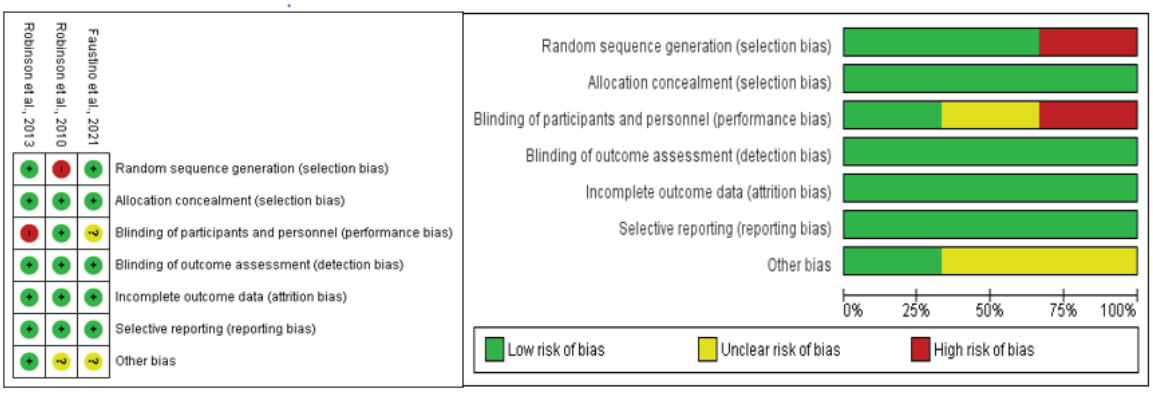

Figure 2. Assessment of risk of bias based on the evaluation domains listed in the Cochrane Collaboration Risk of Bias Tool: risk of bias graph (a) risk of bias summary (b) risk of bias graph

Table 1. Study characteristics of dosing strategy of enoxaparin in critically ill pediatrics

Author and year	Study Design	Study duration	Location	Sample size	Patient characteristics	Treatment/ Prophylaxis	Dosing Strategy		Clinical outcomes
							Initial dosing	Therapeutic dosing	
Diab et al., 2017 (22)	Retrospective study	January 2014 – March 2016	USA	110	Cardiac disease	Treatment and prophylaxis	-	**For therapeutic:** Group 1 >2 months: 1.8 mg/kg/12h IV <2 months: 1 mg/kg/dose IV Group 2 >2 months: 1.8 mg/kg/12h SC <2 months: 1 mg/kg/dose (SC) **For prophylactic:** Group 1 >2 months: 0.75 mg/kg/dose (IV) <2 months: 0.5 mg/kg/dose (IV) Group 2 >2 months: 0.75 mg/kg/dose (SC) <2 months: 0.5 mg/kg/dose (SC)	The anticoagulation with IV infused over 30 minutes is safe and equivalent to SC dosing.
Corder et al., 2014 (15)	Retrospective study	July 2006 – July 2011	Pennsylvania	60	Thrombosis	Treatment	**Group 1** AT3 was administered prior to initiation of dosing. 1.32 ± 0.24 mg/kg SC BID **Group 2** Without AT3 administration 1.32 ± 0.24 mg/kg SC BID	1.51±0.22 mg/kg SC BID	Supplementation with AT3 did not decrease time to therapeutic anti-Xa level, added significant cost and was associated with increased bleeding events.
Malowany et al., 2007 (13)	Retrospective study	January 1998 – June 2006	Canada	16	Thrombosis	Treatment	1.41 ± 0.15 mg/kg SC BID	1.92 ± 0.43 mg/kg SC BID	56% infants experienced side effects at the site of indwelling SC catheter Initial dosing is likely to inadequate to obtain therapeutic levels for neonates.
Hicks et al., 2012 (14)	Retrospective study	January 2002 – October 2010	USA	33	Mixed	Treatment	1.4 mg/kg SC BID	2.0 mg/kg SC BID	A higher initial dose of enoxaparin is required than suggested by guidelines.

Bennett et al., 2022 (16)	Retrospective study	January 2016 – December 2018	USA	194	Venous thromboembolism	Prophylaxis	0.75 mg/kg/dose SC BID	1.04 ± 0.25 mg/kg SC BID	5.6% of patients developed VTE. Anti-Xa level directed strategy of prophylactic enoxaparin is suggested.
De Toledo et al., 2010 (4)	Retrospective study	January 2005 – December 2007	USA	31	Thromboembolism	Treatment and prophylaxis	Patients with abnormal Clcr 0.8-1.8 mg/kg/12h Older patients: 1.1 – 1.3 mg/kg/12h	Patients with abnormal Clcr 1-2.9 mg/kg/12h Older patients: 1.7 – 1.9 mg/kg/12h	Initial high dosing of enoxaparin is required to achieve target anticoagulation.
Schloemer et al., 2014 (17)	Retrospective study	January 2005 – December 2010	West Indies	192	Thromboembolism	Treatment	1.11 – 1.13 mg/kg/12h	< 2months 1.5 mg/kg/12h <2 months – 1 year 1.37 mg/kg/12h 1 year- 13 years 1.01 mg/kg/12h	A higher dose of enoxaparin is required to achieve the recommended strategy.
Streetz et al., 2019 (23)	Case series	November 2016 – September 2017	USA	3	Venous thromboembolism	Prophylaxis	Patient 1 1 mg/kg/SC every 24h Patient 2 1 mg/kg/SC every 24h Patient 3 1 mg/kg/SC every 24h	Patient 1 0.35 mg/kg/12h IV Patient 2 0.5 mg/kg/12h IV Patient 3 0.35 mg/kg/12h IV	Therapeutic level was achieved with IV doses ranging from 0.35 to 0.5 mg/kg/12h
Brown et al., 2013 (18)	Retrospective study	October 2004 – December 2012	USA	35	Venous thromboembolism	Prophylaxis	0.5 mg/kg/12h	0.6 – 0.625 mg/kg/12 h*	Doses were increased but did not achieve therapeutic level. Higher initial dosing of enoxaparin is required because of altered PK parameters.
Cies et al., 2014 (24)	Case-control	January 2009 – June 2012	USA	45	Mixed	Treatment and prophylaxis	0.31 – 1.5 mg/kg/dose	0.4 – 2.2 mg/kg/dose IV 0.38 – 2.3 mg/kg/dose	30 minutes IV infusion was found to produce therapeutic 4-h anti-Xa level similar to SC dosing.
Robinson et al., 2013 (20)	RCT	-	Denmark	72	Thrombosis	Prophylaxis	**Group 1** 40 mg OD SC for 3 days **Group 2** 30 mg BID SC for 3 days **Group 3** 40 mg BID SC or 1 mg/kg OD for 3 days	-	A weight-based dose yielded the best anti-Xa levels.
Crary et al., 2008 (25)	Retrospective study	April 2005 – March 2006	USA	7	Mixed	Treatment and prophylaxis	-	<1 year of age: 2.40 + 0.58 mg/kg >1 year of age: 1.11 + 0.13 mg/kg	The IV administration is safe and effective. Further studies are required.

Bohnhoff et al., 2017 (19)	Retrospective study	2005 - 2013	USA	26	Venous Thrombosis	Treatment	1.5 mg/kg/12h	2.1 mg/kg/12h	The most NICU patients with venous thrombosis require enoxaparin doses higher than suggested dose by ACCP
Faustino et al., 2021 (26)	RCT	November 2017 – August 2019	USA	51	Catheter-associated deep venous thrombosis	Prophylaxis	< 2 months: 0.75 mg/kg/12h SC >2 months: 0.5 mg/kg/12h SC	-	The reduction in risk of CADVT with prophylaxis is limited to older children. Therapeutic doses should be tested to reduce risk of CADVT in critically infants
Robinson et al., 2010 (21)	RCT	February 2006 – March 2009	Denmark	32	Mixed	Treatment	Group 1: 40 mg SC for 24 h Group 2: 50 mg SC for 24 h Group 3: 60 mg SC for 24 h Group 4: 70 mg SC for 24 h	-	Higher doses result in better peak anti-Xa levels with a ceiling effect observed at 60 mg

AT3= Antithrombin III, SC: Subcutaneous. IV: Intravenous, BID: Twice a day, CADVT: Catheter associated deep venous thrombosis. QID: Four times a day, NICU: Neonatal Intensive care units, PK: Pharmacokinetics, Clcr: Creatinine clearance, *=Calculated value, ACCP: American College of Chest Physicians.

administration may be a viable alternative to SC administration in certain cases. Malowany et al., 2007 performed a retrospective study included 16 patients with thrombosis. The study found that the initial dosing of enoxaparin was likely inadequate to achieve therapeutic levels for neonates, and 56% of infants experienced side effects at the site of the indwelling SC catheter. De Toledo et al., 2010 included 31 patients in retrospective study with thromboembolism. The authors recommended an initial high dosing of enoxaparin to achieve target anticoagulation, especially for patients with abnormal creatinine clearance (Clcr). Robinson et al., 2013 conduced a randomized controlled trial (RCT) included 72 patients with thrombosis and compared different dosing regimens for prophylaxis. The study concluded that a weight-based dose yielded the best anti-Xa levels. (Table 2)

Clinical Outcomes

Various clinical outcomes were assessed across the studies. These outcomes included time to therapeutic anti-Xa levels, bleeding events, side effects, and the development of venous thromboembolism. The results were heterogeneous, with different factors influencing clinical outcomes. For instance, supplementation with antithrombin III (AT3) did not significantly decrease time to therapeutic anti-Xa levels and was associated with increased bleeding events.[15] Additionally, Faustino et al. (2021) suggested that therapeutic doses of enoxaparin should be explored to reduce the risk of catheter-associated deep venous thrombosis (CADVT) in critically ill infants. The measurement of anti-Xa levels served as an indicator of therapeutic efficacy in several studies. Some studies recommended an anti-Xa level-directed strategy for prophylactic enoxaparin.[16] Robinson et al.

Table 2. Quality assessment of included studies by NOS

	Selection				Comparability	Outcomes			
Reference	**Representative of sample[A]**	**Selection of sample [B]**	**Ascertainment of exposure[C]**	**Outcomes of interest is not present at the start of study**	**Comparability of studies on basis of design[E]**	**Assessment of outcomes[F]**	**Follow-up[G]**	**Adequacy of follow-up**	**Quality Score**
Diab et al., 2017 (22)	*	*	*	*	*	*	*	-	7
Corder et al., 2014 (15)	*	*	*	*	**	*	*	-	8
Malowany et al., 2007 (13)	*	*	*	*	*	*	*	*	8
Hicks et al., 2012 (14)	*	*	*	*	**	*	*	-	8
Bennett et al., 2022 (16)	*	*	*	*	*	*	*	-	7
De Toledo et al., 2010 (4)	*	*	*	*	**	*	-	-	7
Schloemer et al., 2014 (17)	*	*	*	*	**	*	-	-	7
Brown et al., 2013 (18)	*	*	*	*	**	*	-	-	7

Crary et al., 2008 (25)	*	*	*	*	**	*	*	-	8
Bohnhoff et al., 2017 (19)	*	*	*	*	*	*	*	*	8

A: *=truly representative or somewhat representative of average in target population
B: *=Drawn from the same community
C: *=Secured record or structured review
D: *=Yes, - = No
E: *= Study controls for age, gender, and other factors.
F: *=Record linkage or blind assessment, **=Both
G: *=follow-up of all subjects

(2013) found that a weight-based dose yielded optimal anti-Xa levels. These findings underscore the importance of monitoring anti-Xa levels to ensure therapeutic efficacy and adjust dosing as needed. Bennett et al., 2022 conducted a retrospective study of 194 patients with venous thromboembolism, the authors suggested an anti-Xa level-directed strategy for prophylactic enoxaparin. They found that 5.6% of patients developed venous thromboembolism. (Table 3)

Meta-analysis

Of 15 studies, only six studies reported mortality outcomes.[13,17-21] Overall, 5.8% (22 of 373 patients) were died. No heterogeneity between studies was observed between these studies. After receiving therapeutic dose for prophylaxis, a total of 13 patients experienced thrombotic events (RR = 0.06, 95% CI = 0.03 – 0.09).[16,18] The frequency of bleeding events was observed in 20 patients (I2= 39%, RR=0.03, 95% CI = 0.01 – 0.06).[13-16,21,22]

DISCUSSION

Enoxaparin is usually prescribed for the prevention and treatment of multiple conditions such as DVT, pulmonary embolism (PE), atrial fibrillation, and acute coronary syndromes.[29,30] The recommended dose of enoxaparin in pediatrics ranges from 0.5 to 1.5 mg/kg/12h for prophylaxis of VTE and 1 – 1.5 mg/kg/12h for the treatment of DVT and PE.[31-33] However, majority of the studies reported that the initial recommended dose is insufficient to achieve therapeutic levels.[4,13,17,19,22] A study reported that pediatrics younger than one year of age required a high enoxaparin dose of 1.5 – 2.7 mg/kg/12h administered subcutaneously.[34]The standard mode of administering enoxaparin is via subcutaneous (SC) route, but three studies reported that the enoxaparin dosing via IV route is safe and equivalent to SC dosing.[22-24] However, in some cases, the selection of an appropriate route for administering enoxaparin depends on multiple factors such as the severity of the condition, patient's stability, and the presence of any drug-drug interaction. Due to its easy-to-use feature and lower risk of infection compared to IV route, the SC route is typically used for administering enoxaparin in critically ill pediatric patients. Limited data is available on the utilization of enoxaparin via IV route in several conditions such as DVT, thromboembolism and hemodialysis.[23,25] (figure 3)

Overall, only six studies reported the mortality rates for the patients who receive enoxaparin for prevention and treatment and this review found no significant association between studies.[5,13,17-19,21] Similarly, Young et al., conducted a systematic review that assessed the safety and efficacy of enoxaparin for thromboprophylaxis in critically ill pediatrics.[36] No significant difference in mortality rate was found between patients receiving enoxaparin and those receiving standard care or other therapy for thromboprophylaxis. However, it should be taken into consideration that mortality was not the primary outcome in most of these studies. In terms of specific enoxaparin dosing and mortality rate, limited data exist. (Table 4)

Dosage regimens for enoxaparin in critically ill pediatric patients are often extrapolated from adult dosing guidelines or

Table 3. Quality assessment of case series by JBI (27)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall assessment
Streetz et al., 2019 (23)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk

Q1. Were there clear criteria for inclusion in the case series?
Q2. Was the condition measured in a standard, reliable way for all participants included in the case series?
Q3. Were valid methods used for the identification of the condition for all participants included in the case series?
Q4. Did the case series have consecutive inclusion of participants?
Q5. Did the case series have complete inclusion of participants?
Q6. Was there clear reporting of the demographics of the participants in the study?
Q7. Was there clear reporting of the clinical information of the participants?
Q8. Were the outcomes or follow-up results of cases clearly reported?
Q9: Was there clear reporting of the presenting sites/clinics' demographics?
Q10: Was statistical analysis appropriate?

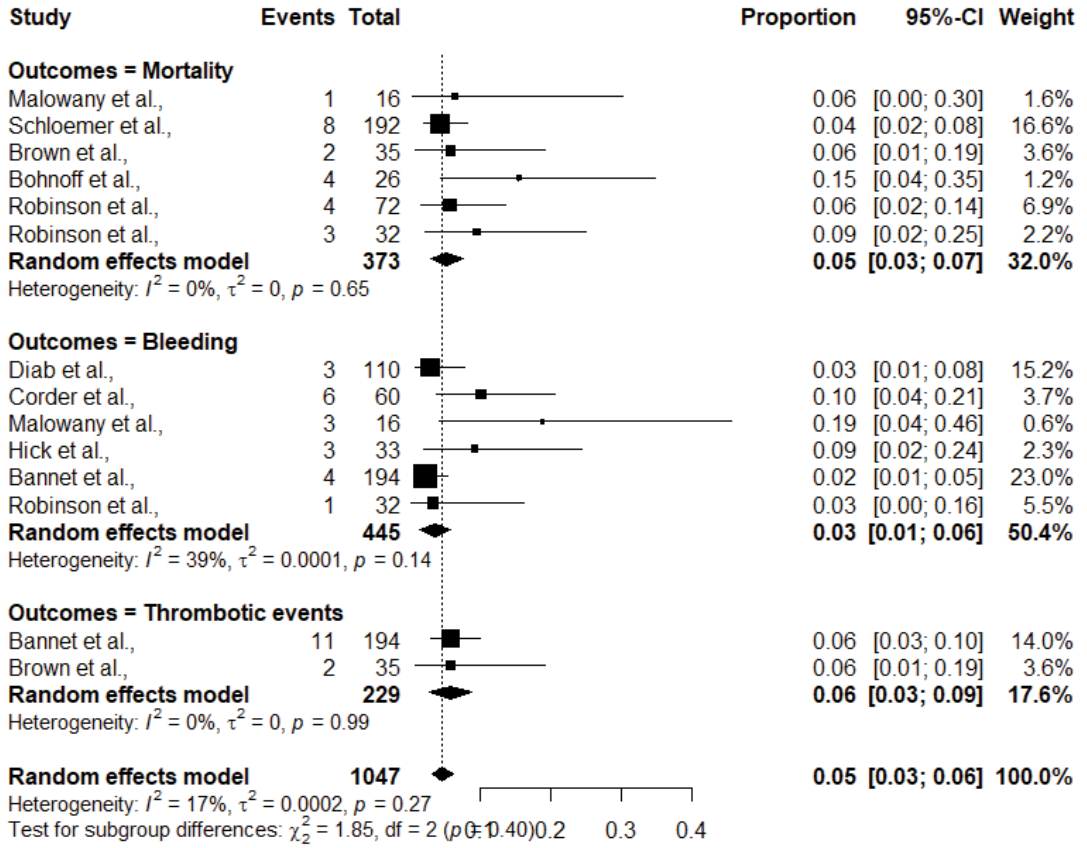

Figure 3. Forest plot of outcomes of dose adjustment

Table 4. Quality assessment of case controls by JBI (28)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall assessment
Cies et al., 2014 (24)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low risk

Q1. Were the groups comparable other than the presence of diseases in cases or the absences of disease in controls?
Q2. Were case and control matched appropriately?
Q3. Were the same criteria used for the identification of cases and controls?
Q4. Was exposure measured in a standard, valid and reliable way?
Q5. Was exposure measured in a same way for case and control?
Q6. Were confounding factors identified?
Q7. Were strategies to deal with confounding factors stated?
Q8. Were outcomes assessed in a standard, valid and reliable way for cases and control?
Q9. Was the exposure period of interest long enough to meaningful?
Q10: Was appropriate statistical analysis used?

determined based on age and weight-based calculations.[37]There is a lack of large-scale clinical trials specifically focusing on the impact of enoxaparin dose on the mortality rate in this population.[38] It is worth noting that enoxaparin, like any anticoagulant, carries a risk of bleeding complications. In this review, only seven studies reported bleeding events.[13-16,21,22] Excessive anticoagulation can lead to bleeding events, which can impact mortality rates.[39] Therefore, careful monitoring of anti-factor Xa levels and appropriate dose adjustments are crucial to maintain a balance between thromboprophylaxis and bleeding risk. Existing literature has documented various side effects associated with enoxaparin administration, including GIT bleeding, thrombocytopenia, epistaxis, bleeding from oral mucosa. Interestingly, these side effects do not correlate with high anti-Xa levels.[40] However, Malowany et al., also reported osteopenia and scleral hemorrhage along with bleeding

events.[13]

The incidence of DVT in pediatrics is still lower than adults, but the risk cannot be overlooked. It is challenging to identify risk factors associated with DVT and VTE. The existing literature lacks a consensus regarding which pediatric patients should receive enoxaparin for prophylaxis. Of nine studies, seven studies did not report any thrombotic events in patients who receive enoxaparin for prophylaxis.[4,20,22-26] Branchford and his colleagues reported that systemic infection, mechanical ventilation and hospital stay exceeding 5 days were identified as an independent risk factors for developing VTE.[41] Furthermore, another study reported that deep sedation, parenteral nutrition, inotropic support, neuromuscular blockade and recombinant factor VIIa administration increase the risk of pediatric trauma patients.[1] Therefore, prophylaxis will reduce these risk factors and prevent VTE and DVT.

Limited data are available on the pharmacokinetics (PK) and pharmacodynamics (PD) of enoxaparin in critically ill patients.[42] To the best of our knowledge, no study is reported on the PK and PD parameters of enoxaparin in critically ill pediatrics. The recommended individualized dosing strategies are based on patient-specific factors.[43,44] Therefore, dose optimization approaches such as therapeutic drug monitoring (TDM) and pharmacokinetic modeling are required for developing dosing algorithms for a drug in pediatrics.[45,46] These approaches consider patients' characteristics such as weight, age, renal function, and coagulation status to estimate individualized doses.[47,48]

This systematic review set certain limitations. Firstly, we identified a mere 15 studies consisting of 10 retrospective studies, 3 RCTs, 1 case series and 1 case-control. The available data might not be sufficient to evaluate the safety and efficacy of enoxaparin dosing, thus, necessitating the additional RCTs. Secondly, although all studies included patients who are critically ill, it is crucial to incorporate more studies with the same timeframe to ensure consistency and minimize treatment bias. Thirdly, there is a lack of comparative data between the control and intervention groups to assess the dosing strategy of enoxaparin.

CONCLUSIONS

This systematic review reported that initial high dose of enoxaparin is required to achieve therapeutic levels. However, limited data regarding dose optimization of enoxaparin is available on critically ill pediatrics. Pharmacokinetic studies, therapeutic drug monitoring, and population pharmacokinetic modelling can guide personalized dosing decisions. The implementation of personalized dosing protocols in clinical practice has the potential to improve patient care, enhance safety, and optimize anticoagulation management in critically ill pediatrics. Further research including prospective studies and RCTs is essential to establish pediatric-specific dosing guidelines and target anti-factor Xa ranges for enoxaparin in critically ill pediatrics.

AUTHOR CONTRIBUTIONS

"Conceptualization, M.K.A., K.B.A., and M.Q.; methodology, M.K.A., M.Q., and A.A.; software, -; validation, M.K.A., W.A., and R.A.; formal analysis, -; investigation, L.A., A.A.-M., and S.A.; resources, R.A., D.A., and R.A.; data curation, R.A., D.A., and R.A.; writing—original draft preparation, M.K.A., K.B.A., and M.Q.; writing—review and editing, M.K.A., K.B.A., and M.Q.; visualization, S.A., R.A., and B.A.-R.; supervision, -; project administration, R.A., R.A., and D.A.; All authors have read and agreed to the published version of the manuscript."

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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