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Comparison of Time Within Therapeutic Range Using Anti-Factor Xa Versus Activated Partial Thromboplastin Time Monitoring of Unfractionated Heparin in Children

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OBJECTIVE To compare unfractionated heparin (UFH) monitoring using time in therapeutic range of activated partial thromboplastin time (aPTT) versus anti-factor Xa activity (anti-Xa) in children.

METHODS This retrospective chart review, with data between October 2015 and October 2019, included pediatric patients younger than 18 years on therapeutic UFH infusion with aPTT or anti-Xa monitoring. Patients receiving extracorporeal membrane oxygenation, dialysis, concomitant anticoagulants, prophylactic UFH, no stated goal, and UFH administered for less than 12 hours were excluded. The primary outcome compared the percentage of time in therapeutic range between aPTT and anti-Xa. Secondary outcomes included time to first therapeutic value, UFH infusion rates, mean rate adjustments, and adverse events.

RESULTS A total of 65 patients were included, with 33 aPTT patients and 32 anti-Xa patients, representing 39 UFH orders in each group. Baseline characteristics were similar between groups, with an overall mean age of 1.4 years and mean weight of 6.7 kg. The anti-Xa cohort demonstrated a statistically significantly higher percentage of time in therapeutic range compared with the aPTT group (50.3% vs 26.9%, p = 0.002). The anti-Xa group also demonstrated a trend toward decreased time to first therapeutic value compared with aPTT (14 vs 23.2 hours, p = 0.12). Two patients in each group experienced new or worsening thrombosis. Six patients in the aPTT cohort experienced bleeding.

CONCLUSIONS This study demonstrated greater time was spent within therapeutic range for children receiving UFH monitored with anti-Xa compared with aPTT. Future studies should assess clinical outcomes in a larger population.

ABBREVIATIONS aPTT, activated partial thromboplastin time; anti-Xa, anti–factor Xa activity; UFH, unfractionated heparin

KEYWORDS anticoagulants; heparin; pediatrics; therapeutic drug monitoring; thromboembolism

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Introduction

The incidence of venous thromboembolism in children has increased, reported as a 70% increase between 2001 and 2009. The mainstay of treatment is either unfractionated heparin (UFH) or low-molecular-weight heparin.[1–3] Activated partial thromboplastin time (aPTT) has historically been used to monitor UFH anticoagulation. The most recent CHEST guidelines from 2012 describe that therapeutic aPTT ranges in children should correspond to an anti–factor Xa activity (anti-Xa) of 0.35 to 0.7 units/mL.[3,4] Although aPTT monitoring is lower cost, simple to perform, and broadly available, it is also reported to have wide variability in reagent sensitivity. It is also dependent on other coagulation proteins, such as factor VIII and fibrinogen, and is an acute-phase reactant, which can lead to falsely elevated results in acutely ill children.[5] These potential confounders may affect the accuracy of measurements.

Recent pediatric studies report a poor correlation between aPTT and anti-Xa activity, causing some institutions to shift towards using anti-Xa as the standard assessment parameter for UFH infusions.[4,6,7] Anti-Xa can also be influenced by confounders (hypertriglyceridemia and hyperbilirubinemia) because of its colorimetric assay, but unlike aPTT it allows for a direct measure of UFH inhibition of factor Xa.[8] Historically, anti-Xa is not as broadly available and can be more expensive than using aPTT.

Many children's hospitals have recently changed their monitoring assay to anti-Xa, and it is unclear if this change is associated with improved outcomes in the pediatric population.[6] Available adult data favor the use of anti-Xa because there is less variability of concentrations, fewer rate adjustments, and quicker time to therapeutic range.[9–13] Data in children are limited, with 1 study suggesting similar time to first therapeutic value

Table 1. Baseline Patient Demographics and UFH Data

Patient Demographics	aPTT (n = 33)	Anti-Xa (n = 32)	p value
Age, median (IQR), yr	0.5 (0–2)	1 (0–2)	0.45
<1 yr, n	13	16	
1–3 yr, n	16	13	
>3 yr, n	4	3	
Female sex, n %	15 (45)	16 (50)	0.71
Weight, median (IQR), kg	4.8 (3.5–6.9)	5.4 (3.5–7.5)	0.54
Race or ethnicity, n %			
White (non-Hispanic)	17 (52)	12 (38)	0.83
African American	4 (12)	5 (16)	
Asian	2 (6)	3 (9)	
Hispanic	9 (27)	10 (31)	
Other	1 (3)	2 (6)	
UFH indication*			
New thrombus	14	12	N/A
Valve replacement	3	2	
Shunt or stent placement	5	3	
Warfarin bridge	1	4	
Diminished LE pulses	11	13	
Other	5	5	
Duration of UFH Infusion, median (IQR), days	3 (2–5)	3 (2–5.3)	0.49

anti-Xa, anti–factor Xa; aPTT, activated partial thromboplastin time; LE, lower extremity; N/A, not applicable; UFH, unfractionated heparin

* Data representing individual orders, rather than numbers of patients.

with either assay.[14]

At our institution, UFH monitoring was adjusted in October 2017 from aPTT to anti-Xa for improved laboratory accuracy with less reagent variability. In order to assess the effects of this change in UFH monitoring, the objective of this study was to compare the percentage of time in therapeutic range between aPTT and anti-Xa for therapeutic UFH monitoring in pediatric patients.

Materials and Methods

Study Design. This was a single-center, retrospective cohort study conducted at a large academic medical center (121-bed children's hospital within a hospital). Patients younger than 18 years who received UFH at therapeutic dosing with measured aPTT values between October 3, 2015, and October 2, 2017 (prechange), and measured anti-Xa values between October 3, 2017, and October 3, 2019 (postchange) were included. Patients who received extracorporeal membrane oxygenation, continuous renal replacement therapy, anti-thrombin replacement therapy, concomitant anticoagulants and/or bridging, prophylactic UFH and/or low-molecular-weight heparin, UFH administered less than 12 hours, and UFH orders without stated aPTT or anti-Xa goal were excluded. A generated report of UFH infusion orders on all pediatric units was screened for eligibility based on the stated inclusion and exclusion criteria. Multiple orders on individual patients were included if part of different encounters or therapeutically independent, defined as having been off UFH infusion for at least 24 hours. The shared electronic medical record was used for further screening of eligibility as well as data collection.

Patient demographic data included sex, race, weight, and age. The UFH indication, minimum and maximum UFH rate, total days of UFH therapy, total number of aPTT or anti-Xa values, total number of therapeutic values, hours within therapeutic range defined as from first therapeutic value to next non-therapeutic value, hours to first therapeutic value, rate of UFH when therapeutic, and potential confounders for non-therapeutic values (bilirubin, triglyceride, noted clotting factor deficiency, and antithrombin) were assessed. Data were collected for a given UFH order until the infusion was either discontinued or the target aPTT or anti-Xa was adjusted. Laboratory-defined therapeutic ranges for aPTT were determined and updated with each new reagent batch using the Brill-Edwards curve. The targeted ranges were patient specific, but most commonly they were 45 to 55, 50 to 70, and 75 to 100 seconds for aPTT and 0.2 to 0.4 units/mL or 0.3 to 0.7 units/mL for anti-Xa.

End Points. The primary outcome of this study was to compare the percentage of time the aPTT and anti-Xa values were in therapeutic range while on UFH. Therapeutic range, for the purposes of this study, was defined as the goal aPTT or anti-Xa value that was being targeted for a given patient. Secondary outcomes

Table 2. Secondary Outcomes

UFH Data or Clinical Outcomes	aPTT (n = 33)	Anti-Xa (n = 32)	p value
Minimum rate, median (IQR), units/kg/hr	14 (10–20)	20 (10–25)	0.038
<1 yr old	14.1	19.2	
1–3 yr old	14.5	19.2	
>3 yr old	17.5	20	
Maximum rate, median (IQR), units/kg/hr	25.3 (20–31)	28 (20–32)	0.51
<1 yr old	26.7	29.1	
1–3 yr old	25.4	28.4	
>3 yr old	29.5	24.7	
Therapeutic rate, mean ± SE, units/kg/hr †	17.9 ± 1.81	22.1 ± 1.81	0.13
<1 yr old	18.8	23.8	
1–3 yr old	16.3	20.2	
>3 yr old	23.5	22.7	
Hours to first therapeutic concentration, mean ± SE	23.2 ± 3.88	14 ± 3.88	0.38
Total rate adjustments mean ± SE	8.9 ± 0.98	3.9 ± 0.98	0.003
Bleeding events	6	0	N/A
Major	3	0	
Minor	3	0	
Thrombosis during therapy	2	2	N/A

anti-Xa, anti–factor Xa; aPTT, activated partial thromboplastin time; N/A, not applicable; UFH, unfractionated heparin

included mean time to first therapeutic value, mean minimum UFH rate, mean maximum UFH rate, mean UFH rate when first therapeutic, mean rate adjustments, and select adverse events (major or minor bleeding events, new or worsening thrombus).

For adverse events, bleeding events were confirmed via progress notes in the electronic medical record and new or worsening thrombus was confirmed by imaging. If a bleeding event was noted, hemoglobin and blood pressure before and after UFH infusion, number of blood transfusions (administered based on clinical judgment), and imaging studies were collected. Bleeding events were defined based on International Society on Thrombosis and Haemostasis classifications, with major bleeding involving either a 2 g/dL (20 g/L) or more decrease in hemoglobin, 2 or more transfusions of red blood cells or whole blood, or death due to bleeding event.[15] A decrease in systolic blood pressure of 20 mm Hg or more was also included in the major bleeding criteria to assess for hemodynamic instability associated with bleeding.

Statistical Analysis. For statistical analysis, mean (SE), median (IQR), and percentages were used to describe summary demographic and clinical data. Fisher exact test and χ^2 test were used for categoric variables and Wilcoxon rank sum was used for non-parametric continuous variables. Mixed-effects analysis of variance models were used to test for treatment differences in percentage of time in therapeutic range, time to first therapeutic dose, and total rate adjustments to control for multiple observations and admissions per patient. Time to first therapeutic dose was log transformed to achieve normality. Sample size was dependent on available patients between the conversion to anti-Xa monitoring and Institional Review Board approval. A p value of less than 0.05 was considered statistically significant.

Results

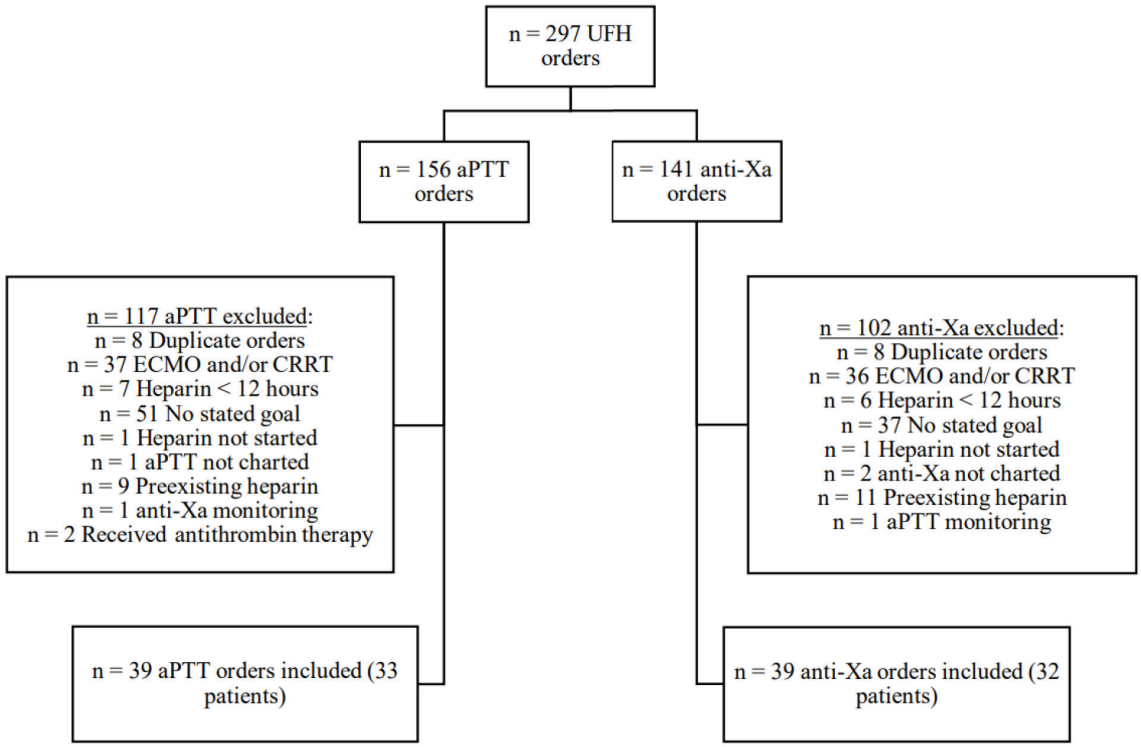
A total of 297 UFH infusion orders were screened for eligibility. Of the 297 initial orders, 156 were in the aPTT group and 141 in the anti-Xa group. Because of exclusion criteria, 117 UFH orders for aPTT and 102 UFH orders for anti-Xa were excluded (Figure 1), leaving 39 orders in each group. These orders encompassed a total of 65 patients in the final analysis, with 33 patients in the aPTT group and 32 patients in the anti-Xa group. Approximately 84% (55) of patients had 1 infusion order, 11% (7) had 2, and 5% (3) had 3 orders.

Among included patients, the mean age was 1.4 years (1 month to 9 years). The mean weight was 6.7 kg (1–24). Females comprised 48% of the entire sample. Baseline patient demographic information between cohorts is shown in Table 1. No statistically significant differences in demographics were noted between the 2 groups.

The primary outcome of mean percentage of time within therapeutic range is shown in Figure 2. The anti-Xa cohort had a statistically significant greater mean ± SE percentage of time within therapeutic range than the aPTT cohort (50.3 ± 0.043 vs 26.9 ± 0.043, p = 0.002).

Secondary outcomes are shown in Table 2. Although not statistically significant, patients in the anti-Xa cohort reached therapeutic range sooner (14 ± 3.88

Figure 1. Flow diagram of included unfractionated heparin orders.



anti-Xa, anti–factor Xa activity; aPTT, activated partial thromboplastin time; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; UFH, unfractionated heparin.

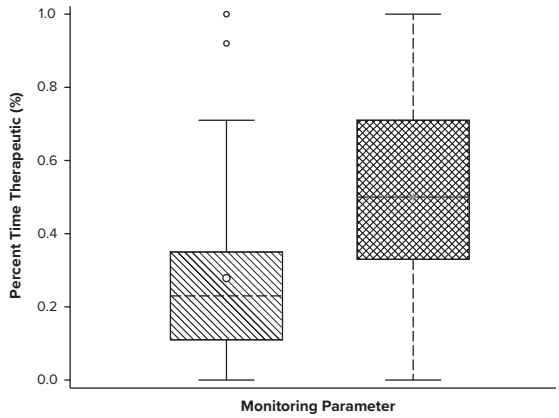
hours) compared with aPTT (23.2 ± 3.88 hours, p = 0.38). A higher therapeutic mean infusion rate was seen in the anti-Xa group (22.1 ± 1.81 units/kg/hr) vs the aPTT group (17.9 ± 1.81 units/kg/hr, p = 0.13), which was also not statistically significant. Median minimum and maximum UFH infusion rates were higher in the anti-Xa cohort, with higher minimum rate being statistically significant (20 [IQR, 10–25] vs 14 [IQR, 10–20] units/kg/hr; p = 0.038). The median maximum rates trended higher in the anti-Xa group (28 [IQR, 20–32] vs 25.3 [IQR, 20–31]; p = 0.51). There were statistically significantly fewer mean rate adjustments to the UFH infusion in the anti-Xa cohort compared with aPTT (3.9 ± 0.98 vs 8.9 ± 0.98; p = 0.003). Both treatment groups had 2 patients each with new or worsening thrombosis on UFH therapy. The only bleeding events (3 major and 3 minor) occurred in the aPTT cohort.

Discussion

Limited data regarding optimal UFH monitoring in children have led to questions regarding best practices in assay selection. The available data in adults tend to favor the use of anti-Xa monitoring, with decreased variability, fewer rate adjustments, and quicker time to therapeutic range.[9–13] In this study, we demonstrated pediatric patients monitored with anti-Xa at our institution had statistically and clinically significant higher percentage of time in therapeutic range compared with those monitored with aPTT.

Available pediatric literature assessing anti-Xa and aPTT monitoring assays is limited. Trucco et al[14] assessed time to first therapeutic value in patients ages 21 years and younger with both assays and found no significant difference. Our primary outcome of time within therapeutic range adds a novel end point to the limited literature evaluating anti-Xa monitoring in the pediatric population. Although time to first therapeutic value is clinically important, time within therapeutic range is also an important data point that represents overall duration of therapeutic effect. This addresses concerns of subtherapeutic or supratherapeutic values that could contribute to either treatment failure or higher risk of bleeding, although data regarding this area are lacking.[16] The increased time in therapeutic range, combined with lower incidence of bleeding in the anti-Xa cohort, possibly represents a more stable and reliable monitoring parameter for UFH infusions. In addition, assessing time within therapeutic range provides a more time-oriented outcome that is applicable to clinical practice, where a more prolonged duration of therapeutic time is of primary concern.

Figure 2. Comparison of least-squares means ± SE of percentage of time within therapeutic range. Center line: median. Center shape (circle or cross): mean. Box: 25th–75th percentile. Bottom whisker: minimum. Top whisker: maximum, excluding outliers. Dots above box: outliers, as defined by more than 1.5 times the IQR beyond the upper quartile.



anti-Xa, anti–factor Xa activity; aPTT, activated partial thromboplastin time.

aPTT; anti-Xa

Other findings include a statistically significantly higher minimum infusion rate, as well as a trend toward higher mean therapeutic infusion rate for the anti-Xa group compared with the aPTT cohort. The higher infusion rates may be due to increased use over time of UFH order sets that recommend appropriately higher doses for younger patients, for example, 28 units/kg/hr for infants compared with 15 to 20 units/kg/hr in older children. Additional findings from our study suggest the anti-Xa monitoring cohort required statistically and clinically significantly fewer rate adjustments during therapy (3.9 vs 8.9, p = 0.003) and reached therapeutic range more quickly compared with the aPTT monitoring cohort (14 vs 23.2 hours, p = 0.38). Although the time to first therapeutic concentration was not statistically significant, it represents a clinically meaningful trend. These findings are consistent with adult data noting fewer rate adjustments and a quicker time to therapeutic range when monitoring UFH therapy with the anti-Xa assay. Depending on institutional factors, there may be a potential for decreased costs associated with anti-Xa monitoring if fewer blood draws are needed, as well as fewer instances of line access and subsequent infection risk, although that was outside the scope of this study.

Despite higher infusion rates, there were no significant bleeding events in the anti-Xa cohort compared with 6 events in the aPTT group. Only 2 patients in each group had new or worsening thromboses while on UFH therapy. *Post hoc* assessment of bleeding episodes using the more recently developed Bleeding Assessment Scale in Critically Ill Children criteria was consistent with the *a priori* definition in classifying bleeding episodes.[17] Based on these criteria, 3 patients still qualified as severe bleeding as a result of a greater than 20% decrease in hemoglobin from baseline. Upon further review, none of the patients had concentrations outside the therapeutic range to explain these findings. This study was not powered to assess clinical outcomes, so caution in interpreting this data is warranted. In addition, patients had a variety of targeted ranges because therapeutic values were defined in our study as being within the ordered goal. The actual targeted range was patient specific and determined based on a given patient's clinical status, bleeding risk, and indication for therapy. This enhances external validity because the therapeutic targets were patient specific and not representative of a singular UFH goal.

Recent data by Saini et al[18] obtained simultaneous anti-Xa and aPTT in 95 patients and found that peak anti-Xa and peak aPTT values were not predictive of major or minor bleeding. Because patients in our study monitored with anti-Xa had fewer rate adjustments and spent more time in the therapeutic range, it may suggest that the lower risk of supratherapeutic values and excess variability would lead to a more stable therapy and potentially fewer bleeding events, without an increase in worsening thromboses. These findings should prompt future studies to investigate infusion rate and safety outcomes in pediatric patients on UFH being monitored with the anti-Xa monitoring assay, given our small sample size and inadequate power to detect differences in safety outcomes.

Limitations of our study include the retrospective nature and the pre- and post-study design. This may confound data with temporal differences during historical treatment periods, including use of aPTT and anti-Xa assays, as well as biases inherent to observational studies. These include incorrect documentation of goals for respective UFH monitoring assays and deviations from the institution's UFH infusion monitoring policy, such as incorrect rate adjustments based on resulted values or when providers request rate changes outside of the normal titration schedule. Administration of bolus doses was not collected as a data point because it is rarely used per institutional practice outside of extracorporeal membrane oxygenation cannulation or pulmonary embolism, which may confound time to first therapeutic value. Another potential limitation was increased use of heparin order panels, which may explain the higher infusion rates in the anti-Xa cohort due to improved dosing recommendations based on patient age. Lastly, our small sample size limits the interpretability of any clinical outcomes, which should be addressed by larger, prospective studies to achieve adequate power.

Conclusion

In summary, we report a retrospective cohort study in which children receiving UFH monitoring using the anti-Xa assay experienced a statistically and clinically significantly greater time within therapeutic range compared with aPTT. Additionally, a trend towards shorter time to first therapeutic value was also observed in the anti-Xa group. Prospective studies comparing both monitoring assays are required to further assess clinical outcomes in the pediatric population.

Article Information

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Ethical Approval and Informed Consent. Institutional Review Board approval with waived consent was obtained prior to data collection, given the retrospective nature of the study.

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Note Added in Proof. As reported more recently by O'Brien et al, the rate of venous thromboembolism in children continues to rise with a 130% increase in cases between 2008 and 2019. Evaluating optimal treatment and monitoring modalities will continue to be vital to appropriate pediatric care.
(O'Brien SH, Stanek JR, Witmer CM, Raffini L. The continued rise of venous thromboembolism across US Children's Hospitals. *Pediatrics*. 2022;149(3):e2021054649.)

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