Lack of correlation between heparin dose and standard clinical monitoring tests in treatment with unfractionated heparin in critically Ill children

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The study was supported by a grant-in-aid from the Canadian Institutes Of Heath Research (MOP 77742) and by an "Erwin Schroedinger-Auslandsstipendium" from the Austrian Science Fund (FWF), Project # J-2038 (S.K). Stefan Kuhle is the recipient of the Baxter BioScience Pediatric Hemostasis Fellowship 2002/2003 at the Hospital for Sick Children, Toronto.

Manuscript received August 28, 2006.
Manuscript accepted January 12, 2007.

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ABSTRACT

The activated partial thromboplastin time (aPTT) and anti-Xa activity are used for monitoring unfractionated heparin (UFH) therapy in children and may not be optimal. Objective: Determine correlations of aPTT, anti-Xa and UFH dose in children. Single centre prospective cohort study in children receiving UFH. The aPTT and anti-Xa results from routine coagulation monitoring were collected. Thirty-nine children (median age 18 days) were enrolled. There was no relationship between aPTT and UFH dose (r^2=0.12) or anti-Xa and UFH dose (r^2=0.03) or aPTT and anti-Xa (r^2=0.22). aPTT and anti-Xa do not accurately monitor UFH therapy in children.

Key words: unfractionated heparin, children, monitoring.

Haematologica 2007; 92:554-557

Unfractionated heparin (UFH) is still required in a large number of children due to its potential for rapid reversal by protamine administration making it the drug of choice in high risk situations such as post-operative congenital heart disease.[1] Close monitoring and optimal dosing of UFH is extremely important because of the critical clinical indications for UFH therapy in pediatrics. The clinical practices in adults of routinely monitoring UFH by the activated partial thromboplastin time (aPTT) and anti-Xa activity have been extrapolated for pediatric use.[2] However, as the aPTT and anti-Xa activity assays were developed on the basis of adult hemostatic systems, they may not be optimal for children due to fundamental differences between the coagulation systems of adults and children.[3-5] Data showing that thrombin-generation based tests overestimate the effect of UFH in newborn plasma.[6] Conversely, tests based on the neutralization of exogenous factor Xa by the antithrombin (AT) heparin-complex, such as the anti-Xa activity assay, underestimate heparin concentrations due to a lower AT activity in newborns.[7] However, these observations are based on studies in which UFH was added to plasma *in vitro*. Relatively recently, assays have been made available for measuring heparin levels such as AT-free anti-Xa assays and automated thrombin clotting time (TCT) based assays and there is a biological rationale why these assays may better reflect heparin levels. The aim of the current study was i) to assess these relationship of aPTT, anti-Xa heparin levels to heparin dose, and ii) to assess newly available assays that may be more appropriate for monitoring UFH in children.

Design and Methods

The study was a prospective cohort study performed at the Hospital for Sick Children, Toronto, Canada. Children >36 weeks gestational age and ≤18 years of age admitted to the critical care unit and requiring therapeutic doses of UFH for ≥12h were eligible. The study was approved by the hospital's Ethics Review Board. Informed consent was obtained from all children and/or guardians.

Table 1. Determination coefficients (r^2) for the relationship between aPTT, anti-Xa levels and UFH dose (whole group).

	UFH dose	*aPTT*	*Anti-Xa (with AT)*	*Anti-Xa (w/o AT)*	*TCT*
UFH dose	–				
aPTT	0.12	–			
Anti-Xa (with AT)	0.03	0.22	–		
Anti-Xa (w/o AT)	0.06	0.21	0.43	–	
TCT	0.06	0.16	0.28	0.11	–

UFH: unfractionated Heparin; aPTT: activated partial thromboplastin time; TCT: thrombin Clotting Time; AT: antithrombin.

During the study period (4/2002–6/2003), 39 children were enrolled. Fifty-six percent of children (n=22) were males; median age was 18 days (2 days–15.4 years). Sixty-four percent (n=25) of patients were neonates and 18% (n=7) were infants or children. The median weight was 4 kg (2.4-150 kg). The most frequent diagnoses were hypoplastic left heart (38%, n=15), transposition of the great arteries (10%, n=4), and Fallot (8%, n=3). Reasons for administration of UFH included Blalock-Taussig shunt (38%, n=15), venous thrombosis (18%, n=7), pulmonary embolism (8%, n=3) and RV-PA conduit (8%, n=3). Nine patients (23%) suffered a major bleed and 2 patients (5%) developed a new thrombosis during UFH therapy. Details on the clinical outcomes of the cohort have been published in a separate manuscript.[8]

Clinical and laboratory data were collected for each patient. Excess plasma from samples drawn as part of clinical care was aliquoted and frozen at –70°C for batch analysis. Samples were collected from a fresh venipuncture or indwelling lines. Heparinized lines were cleared of heparin following a standard procedure before taking the sample. All blood samples were taken ≥3h after a dose change or renewal of the UFH infusion.The UFH starting dose was 28 U/kg/h in infants < 1 year, and 20 U/kg/h in older children. No UFH bolus was given. Both aPTT and anti-Xa activity were used for monitoring. Dose adjustments were made using a revised version of a previously published nomogram.[1,9] Therapeutic ranges for aPTT and anti-Xa activity were 60 - 85 s and 0.3 - 0.7 U/mL, respectively.

For clinical management, levels of UFH measured by aPTT and anti-Xa assays in the clinical laboratory were used. The assays were performed on a MLA 1400C (Instrumentation Laboratory, Milan, Italy) automated coagulation machine. The aPTT was measured using the Hemoliance Thrombosil assay (Chromogenix, Mölndal, Sweden). Anti-Xa levels were determined using a chromogenic assay with purified human AT added to the dilution buffer (Hemoliance, Beckman Coulter, Fullerton USA). The AT-free anti-Xa assay (Coamatic, Chromogenix, Mölndal, Sweden) and TCT assay (Accuclot, Sigma Diagnostics, St Louis, USA) were performed in the hemostasis research laboratory using an ACL 300+ (Instrumentation Laboratory, Milan, Italy).

Statistical analyses were performed using Stata 9.2 (Stata Corp, College Station, TX, USA). APTT and TCT values above the limit of quantification were set to 250 s and 150 s, respectively. Robust regression analysis with a correction for clusters was used to assess the relationship between UFH dose, aPTT, anti-Xa, and TCT. APTT and anti-Xa levels were categorized as below, within, or above the therapeutic range, and the agreement between the aPTT and anti-Xa levels was assessed using Cohen's κ.

Discussion and Results

There were a total of 627 observations (median 12/patient, range 2-119). Median aPTT (n=626) was 120 s (25->212 s). Two hundred and five (33%) aPTT values were above the limit of quantification (>212 s). Median anti-Xa activity level (AT added back; n=593) was 0.33 U/mL (range 0-1.88). Anti-Xa activity (no AT added back; n=458) was 0.22 U/mL (range 0 - 1.56). Median TCT (n=375) was 83 s (11 - >120). A hundred and sixty (43%) TCT values were above the limit of quantification (>120 s). Median AT levels (n=452) were 0.60 (range 0.06-1.07).

The mean dose of UFH in the overall patient population was 25.3 U/kg/h (SD 8.4). The mean dose of UFH in infants was 27.2 U/kg/h (SD 7.8) and 21.1 U/kg/h (SD 8.1) in older children. There was little association between the laboratory tests and UFH dose (Table 1). Cohen's κ for agreement between the aPTT and anti-Xa activity was 0.10 (95% CI 0.01; 0.19). The aPTT overestimated anti-Xa activity in 397/592 (67%) cases and underestimated anti-Xa activity in 28/592 (5%) cases. Results were similar for the anti-Xa assay with no AT added (κ 0.032 [95%CI -0.001; 0.0651]). The aPTT overestimated anti-Xa activity in 348/458 (76%) cases and underestimated anti-Xa activity in 7/458 (2%) cases. Both tests agreed in only 103/458 (22%) cases.

Exclusion of one patient who contributed 119 observations and of 31 observations where no UFH was administered did not change the correlations. Stratification by age group (neonates vs. non-neonates) overall showed slightly better correlations for the non-neonates (*data not shown*). However, correlations between aPTT or UFH dose and other tests remained weak.

The objectives of the study were to assess the relationship of aPTT, anti-Xa activity and UFH dose in a prospective cohort of unselected pediatric patients receiving UFH as part of routine clinical care. Results showed that the aPTT reflected anti-Xa activity less than 33% of the time and there was no relationship between aPTT and anti-Xa activity (r^2=0.22). The aPTT

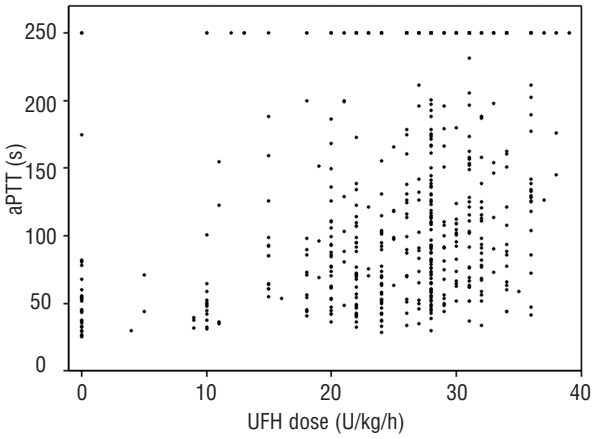

Figure 1. Scatter plot for the relationship of aPTT and unfractionated heparin (UFH) dose (r^2=0.12).

overestimated anti-Xa activity in 67% of cases and underestimated anti-Xa activity in 5%. These data indicate that the aPTT should not be used for routine monitoring children on UFH. More importantly, results from the study show that there was no relationship between heparin dose and either aPTT (r^2=0.12) or anti-Xa activity (r^2=0.03). Nor does standard routine method for clinically monitoring heparin reflect the *in vivo* concentration of heparin in children. A cohort study of UFH in pediatric patients published in 1994 reported that aPTT values and anti-Xa levels matched in 70% of children with the correlation between aPTT and Anti-Xa being r2=0.51(9). These findings were similar to findings in adults, making the extrapolation of adult recommendations for monitoring children acceptable at that time. In fact, the current American College of Chest Physicians (ACCP) guidelines recommended practice dosing for UFH therapy in children is based on this previous study.[1,9] These data contrast sharply with the current study in which over 70% of aPTT values did not match anti-Xa levels and little correlation was seen (r^2=0.22). The difference in the findings probably reflects a change in the patient populations receiving UFH. Over ten years ago, the standard care was to treat children with thrombosis who were relatively clinically uncomplicated with UFH. Today, the standard care is to use LMWH. The use of UFH is restricted to children with clinical complications. Also, children are being successfully managed with far more complicated surgical and medical techniques at a younger age. Therefore, in the current study approximately two-thirds of the children were receiving prophylaxis following surgery for CHD. Only one-third of children were being treated for arterial or venous thrombosis whereas in the previous study two-thirds were being treated. The difference in the patient populations is also indicated by the increased incidence of major bleeding (23%) in these children. The results of the clinical outcomes in this cohort will be published in a separate manuscript.[8]

The relationship of aPTT to heparin level is semi-logarithmic, meaning that as the aPTT increases so too does the sensitivity of the aPTT to heparin.[10,11] Use of aPTT for monitoring heparin, therefore, is based on the assumption that patients' baseline aPTT are comparable to normal controls. This assumption is critical for the linear relationship between heparin and aPTT.[12,13] In the current study, the lack of correlation of aPTT to the heparin dose is probably related to an extreme variation in baseline and, in some children, markedly increased aPTT. When there was no heparin on board in the children, the median aPTT was 56.0 and ranged between 25.2 and >212 so, the aPTT response to heparin would be highly variable. Prolongation of the baseline aPTT reflects the younger age and the relative clinical complexity of the patient population. When correlations were assessed according to age group, correlations between tests and UFH dose were, as expected, somewhat better for non-neonates when compared to neonates. The finding is in keeping with the well-known observation that coagulation parameters tend to vary more in neonates than in older children.[3-5]

Current recommendations in adults are to calibrate the therapeutic range of aPTT by assessing the Anti-Xa and aPTT in at least 30 heparin patients and, by regression analysis, calculate the aPTT range corresponding to target anti-Xa levels.[2,14,15] Applying these recommendations to data from the current pediatric study, the therapeutic aPTT range would be 145-202 s. Therefore, targeting the range recommended with the ACCP guidelines (60-85 s) would under-dose all children.

Two other heparin assays not used routinely in clinical laboratories were assessed in the cohort. The first was an anti-Xa assay, which was designed to be independent of the patients endogenous AT level, and the second was a TCT based assay. The rationale for use of the additional anti-Xa assay was to determine whether an AT independent assay would be a more accurate measurement of heparin levels in children with varying AT levels. The TCT is a fibrin endpoint based assay and is relatively specific for UFH as the assay time is prolonged only in the presence of UFH or fibrinogen abnormalities. Because of the relative specificity to UFH levels, the TCT assay maybe an appropriate test in pediatric patients with large variations in their baseline hemostatic parameters. However, no correlation was seen between either of the assays and the UFH dose. These additional tests do not appear to have any advantage over the standard assay systems.

In conclusion, the current study has identified issues of concern regarding the ability to monitor UFH in children with currently available assays. Results from this study suggest that the aPTT is not suitable for monitoring UFH therapy in severely ill children, as there is no correlation of the aPTT and heparin level. The lack of correlation of the aPTT to heparin dose is probably

related to the increased aPTT values in children with severe underlying disorders. Since publication of the original study which establishing the current recommendations for UFH management, the pediatric patients receiving UFH have become a more clinically complicated population. Finally, and more importantly, the anti-Xa activity does not correlate with heparin dose in children receiving UFH. Therefore, neither test is useful in this population. Studies determining the proper assays for monitoring of UFH therapy in children are needed.

Authors Contributions

SK: responsible for the integrity and analysis of the data, wrote the manuscript; PE: responsible for execution of the research and clinical management of the study patients; BK: responsible for execution of the research and clinical management of the study patients; PM: responsible for execution of the research and clinical management of the study patients; PV: responsible for execution of the research, integrity and analysis of the data; LM: responsible for the conception, design and execution of the research, integrity of the data and analysis of the data, wrote the manuscript.

Conflicts of Interest

The authors reported no potential conflicts of interest.

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