ANDES PEDIATRICA
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Andes pediatr. 2022;93(6):826-831
DOI: 10.32641/andespediatr.v93i6.4271

ORIGINAL ARTICLE

Monitoring of anticoagulant treatment with Unfractionated Heparin in pediatrics

Monitoreo del tratamiento anticoagulante con Heparina no Fraccionada en pediatría

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Received: February 14, 2022; Approved: May 9, 2022

What do we know about the subject matter of this study?

Unfractionated heparin is the most commonly used anticoagulant in pediatric critically ill patients. The American College of Chest Physicians recommends a level of 0.3 - 0.7 units/mL measured by Anti-Xa in the aPTT used for monitoring.

What does this study contribute to what is already known?

It is important to know the correlation between aPTT and Anti-Xa in our pediatric population in order to consider the limitations of aPTT, which is mostly available for unfractionated heparin monitoring in patients at higher risk of bleeding or thrombosis.

Abstract

Unfractionated heparin (UFH) is the most widely used anticoagulant in hospitalized patients. The therapeutic range (TR) was defined in adults according to the prolongation of the activated Partial Thromboplastin Time (aPTT). However, the recommendation is to maintain a therapeutic range with anti-factor Xa assay (antiFXa). As this technique is more complex to perform and less available, it is recommended to make local correlation curves of aPTT with antiFXa. **Objective:** to determine the correlation between the values of aPTT and antiFXa in patients treated with UFH. **Patients and Method:** 52 patients between 2 days to 14 years of age hospitalized in the Pediatric Critical Patient Unit were recruited. They received treatment with UFH in continuous infusion for at least 24 hours. aPTT and antiFXa tests were performed according to the moment of anticoagulation. To evaluate the concordance of the levels of aPTT with those of antiFXa, the Kappa statistical coefficient of Landis and Koch was used. **Results:** 105 samples were collected from 52 patients. The overall concordance was 0.452 (moderate correlation). In patients aged < 1 month (n = 40), a considerable correlation was evident (r = 0.617); in those from 1 month to < 6 months (n = 18) and 6 months - < 12 months with aPTT < 120 seconds (n = 11), also showed a considerable correlation (r = 0.636 and 0.615, respectively), while in those aged > 12 months (n = 37) with aPTT < 120 seconds, a moderate correlation was evident (r = 0.454). **Conclusion:** In our population, there is a moderate correlation between the values of aPTT and antiFXa.

Keywords:
Anticoagulation;
Heparin;
Activated Anti-Factor X;
Partial Thromboplastin Time;
Hemostasis

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Edited by
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How to cite this article: Andes pediatr. 2022;93(6):826-831. DOI: 10.32641/andespediatr.v93i6.4271

Introduction

Anticoagulation with unfractionated heparin (UFH) is widely used in pediatric intensive care units (PICU), given its short half-life and the possibility of reversing its effect with the use of protamine. This is especially important in critical, post-operative, or high-bleeding-risk patients[1]. The success of anticoagulant treatment depends on the accuracy and stability of the indicated dose, which requires adequate monitoring to achieve a therapeutic range (TR) that allows for an adequate anticoagulant effect, with a low risk of bleeding. The TR of UFH was established in the 1970s in clinical studies and was subsequently reaffirmed in animal studies in the 1990s, establishing as TR a value of 1.5 to 2.5 times the value of the Activated Partial Thromboplastin Time (aPTT). These same values have been extrapolated to the pediatric population[2,3], without high-quality evidence to guide the management of anticoagulation in this cohort[4-7].

To date, there are several coagulometers and more than 300 different reagents to perform aPTT, producing a great variability of results[8,9]. On the other hand, some situations interfere with this technique, such as the presence of lupus anticoagulant or congenital or acquired coagulation factor deficiency (liver failure), which determine that its prolongation is not directly related to the activity of circulating heparin (Table 1)[10].

Currently, there are two more specific ways to measure the anticoagulant activity of UFH, one is heparin levels measured in plasma through the Protamine titration technique (TR = 0.2 to 0.4 U/ml) and the other one is Anti Factor Xa (Anti-Xa) values[3,11]. These techniques are the standard for assessing the quality of anticoagulant treatment with UFH. Both are technically more cumbersome and more expensive, so they are less available in PICUs in our country.

The Anti-Xa assay specifically determines the anticoagulant activity of UFH by measuring the ability of heparin-binding antithrombin (AT) to inhibit a single enzyme, factor Xa (FXa). Biological variables that affect the measurement of aPTT such as liver disease, increased level of acute phase reactants, and the presence of lupus anticoagulant, do not interfere with Anti-Xa testing[5,12].

For adults, the current recommendation of the American College of Chest Physicians is to make correlation curves of aPTT with Anti-Xa or Protamine titration, in order to adjust local therapeutic aPTT values and to be able to use aPTT as the first test to monitor UFH use. This correlation was performed in our hospital and confirmed a TR with aPTT values between 50 and 80 seconds[13,14]. In children, the current recommendation of the same organization is to monitor with Anti-Xa since the correlation is more erratic, making it difficult to establish a specific TR[15].

The objective of this work is to determine the correlation between aPTT values and Anti Factor Xa values in pediatric patients hospitalized in the PICU of the UC-Christus Health Network since, despite having the Anti-Xa test available, aPTT is faster and less expensive. In addition, these results could be extrapolated to other PICUs that do not have the Anti-Xa test.

Patients and Method

Pediatric patients between 2 days and 14 years of age, hospitalized in PICU, who received continuous UFH infusion therapy for at least 24 hours, between August 2016 and November 2018, were recruited. Exclusion criteria were patients with known liver disease and those who had an out-of-range baseline aPTT.

The aPTT test was obtained with the HemosIL™ SynthAsil (Instrumentation Laboratory, USA) (Catalog 0020006800) and the Anti-Xa test was performed with the HemosIL™ Liquid Anti-Xa (Instrumentation Laboratory, USA) (Catalog 0020302600).

Table 1. Factors influencing PTT

Preanalytical	Laboratory processing: • Platelet activation should be avoided. (Release of platelet factor 4) • Hemolysis, hyperlipidemia and hyperbilirubinemia
Analytical	Reagent and instrument type: • Variations in the type and concentration of phospholipids in the reagent • Electromechanical or photo-optical coagulometer detection method
Biological factors	• Presence of lupus anticoagulant • Congenital or acquired factor deficiencies (prekallikreins, high molecular weight kininogens, factors XII, XI, IX and/or VIII) • Decreased level of clotting proteins (consumptive coagulopathy or liver disease) • Increased level of acute phase reactants

Blood samples for Anti-Xa were collected by a PICU nurse along with the following routine aPTT sampling, either through venous, arterial, or puncture routes, according to each patient's routine procedure. No extra venous punctures were performed. Tests were obtained according to the time of anticoagulation, and more than one sample could be collected from each patient, with 3 samples maximum. The samples were processed in the emergency laboratory of our hospital. A concordance study was performed to compare the quality of anticoagulation with aPTT in relation to the gold standard Anti-Xa.

To evaluate the concordance of the levels of aPTT with those of Anti-Xa, the Landis and Koch Kappa statistical coefficient was used[16,17], considering a Kappa coefficient between 0.01-0.20 as slight, between 0.21 and 0.40 as acceptable, between 0.41 and 0.60 as moderate, between 0.61 and 0.80 as considerable, and between 0.81 and 1.00 as almost perfect. For data analysis, linear regression and Bland-Altman correlation graphs were created using GraphPad Prism 6 software. Once the general analysis was completed, it was also carried out according to the different age groups.

This study was approved by the Ethics Committee of the *Pontificia Universidad Católica de Chile*. Informed consent was waived since only anonymous samples were analyzed. The Pediatrics Division of the *Pontificia Universidad Católica de Chile* was awarded the funds to cover the expenses of the required laboratory tests.

Results

Between August 2015 and November 2018, 105 samples were analyzed, corresponding to 52 patients. The age range was from 2 days to 14 years; 52% were female and 48% were male (Table 2). The main indications for anticoagulation in our series were post-surgical use for congenital heart disease, the use of a ventricular assist device, and ECMO (Table 2).

When analyzing all the samples, a Kappa coefficient of 0.452 was observed, which represents a moderate correlation (Figure 1).

Subsequently, when analyzing the samples according to age groups, the following was observed:

- Patients younger than 1 month (n = 40) showed a considerable correlation (r = 0.617).
- Patients aged 1 month - < 6 months with aPTT < 120 seconds (n = 18) showed a considerable correlation (r = 0.636) (Figure 2).
- Patients 6 months - < 12 months with aPTT < 120 seconds (n = 11) showed a considerable correlation (r = 0.615).
- Patients older than 12 months (n = 37) with aPTT < 120 seconds showed a moderate correlation (r = 0.454) (Figure 3).

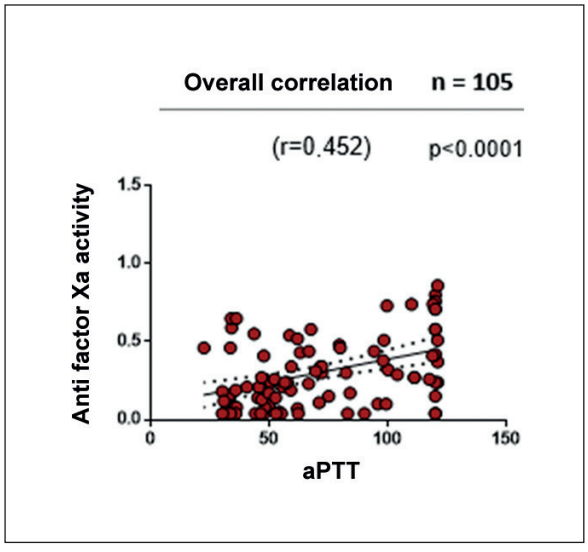

Figure 1. Concordance analysis* between aPTT and AntiFXa values in all patients. *Kappa coefficient (Landis and Koch)[16,17] interprets the strength of concordance of the following parameters: 0.00 poor, 0.01-0.20 slight, 0.21-0.40 acceptable, 0, 41-0.60 moderate, 0.61-0.80 considerable, 0.81-1.00 almost perfect.

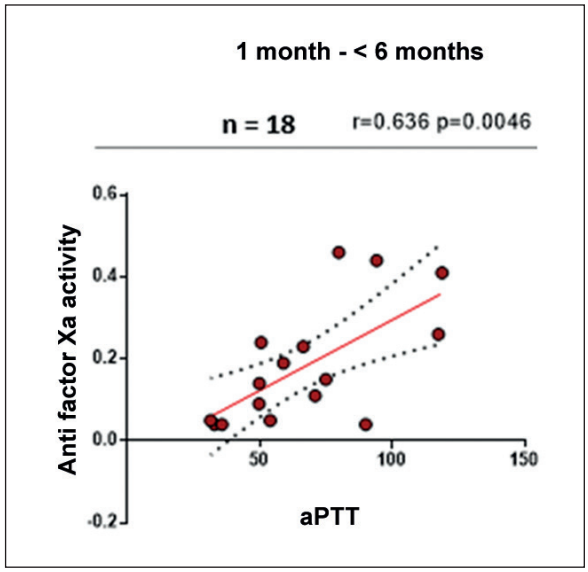

Figure 2. Concordance analysis* in patients 1 month - < 6 months of age. *Kappa coefficient (Landis and Koch)[16,17] interprets the strength of concordance of the following parameters: 0.00 poor, 0.01-0.20 slight, 0.21-0.40 acceptable, 0, 41-0.60 moderate, 0.61-0.80 considerable, 0.81-1.00 almost perfect.

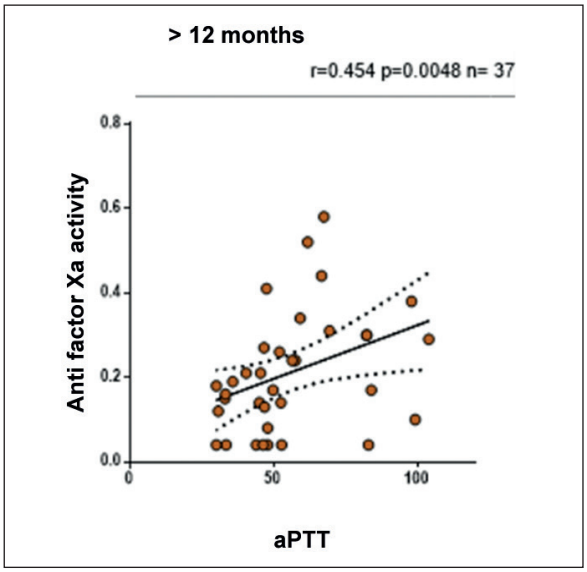

Figure 3. Concordance analysis* in patients older than 12 months. *Kappa coefficient (Landis and Koch)[16,17] interprets the strength of concordance of the following parameters: 0.00 poor, 0.01-0.20 slight, 0.21-0.40 acceptable, 0, 41-0.60 moderate, 0.61-0.80 considerable, 0.81-1.00 almost perfect.

Table 2. Patients characteristics

	n = 52
Age	(2 days old - 14 years)
< 1 month	14 (27%)
1 month - 6 months	13 (25%)
6 months - < 12 months	5 (9.6%)
> 12 months	20 (38.4%)
Gender	
Female	27 (52%)
Male	25 (48%)
Indication of Anticoagulation	
Congenital heart disease - heart surgery	35 (67.3%)
ECMO	9 (17.5%)
Ventricular Assist	5 (9.6%)
Pulmonary hypoplasia secondary to diaphragmatic hernia	2 (3.8%)
Renal artery thrombosis	1 (1.9%)

ECMO: oxigenación por membrana extracorpórea

Discussion

The goal of monitoring the effect of unfractionated heparin is to maximize protection against thrombus progression while minimizing the risk of bleeding[5].

Our results show a moderate correlation of aPTT with Anti-Xa, which is similar to that published by other authors[5,15,18-20]. These results seem reasonable to us, in the context of patients requiring either prophylaxis or therapeutic anticoagulation, with a standard risk of bleeding and a non-critical condition of thrombosis. For the interpretation of these results, it should be considered that the group studied included only patients in a controlled clinical setting, in which the effect of heparin is the only known variable that affected aPTT (see exclusion criteria).

It is noteworthy that in some cases the therapeutic range of Anti-Xa was equivalent to an aPTT of 120 seconds or more. This has already been described by Newall et al.[15], who report that the use of Anti-Xa or protamine titration assays to establish a therapeutic range of aPTT resulted in ranges greater than 200 seconds, concluding that existing methods for determining therapeutic ranges for UFH in adult populations do not produce equivalent ranges in children. Therefore, it is possible that when treating patients in the aPTT ranges suggested for adults (50-80 seconds), we have children in low degrees of anticoagulation[5,19] and, in the case of using Anti-Xa, we are doing so to a greater degree. These differences could partly explain the higher rate of serious hemorrhagic complications reported in children, up to 24%[1,21] compared to 1-11% in adults[22].

In relation to patients aged 1-6 months and 6-12 months, which show a considerable correlation, this could be secondary to the low number of patients we were able to recruit at these ages.

The limitations of this study are related to the difficulty in recruiting patients, which is always complex in the pediatric age, thus affecting the sample size. In addition, despite the exclusion criteria, the enrolled patients had extremely severe pathologies, 5 of them requiring external ventricular assistance and 9 ECMO, which could affect the correlation since hemostasis in these patients is complex and is altered by many factors such as endothelial damage, systemic inflammation, multiorgan failure, among other; however, this could also be a strength since most patients managed with UFH have complex conditions.

Wide availability, automation, and rapid turnaround time have popularized aPTT to monitor heparin doses within a narrow therapeutic range[8,12,15]. However, this test is influenced by preanalytical, analytical, and biological variables that do not reflect heparin activity *in vitro*[23,24].

Finally, in the absence of clinical trials validating any laboratory measure of UFH effect or concentration in terms of clinical efficacy and safety in children, a single assay cannot possibly be recommended and local availability should also be considered.

In conclusion, there is a moderate correlation between aPTT and Anti-Xa values in pediatric patients on continuous UFH infusion therapy, making the use of aPTT alone or ideally in association with Anti-Xa, an adequate tool for monitoring UFH therapy in most patients. However, the overlapping of Anti-Xa values in range and extremely high values of aPTT reaffirms that current UFH monitoring strategies extrapolated from adult practice are possibly inappropriate for children.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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