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Full Length Article

Agreement between activated partial thromboplastin time and anti-Xa activity in critically ill patients receiving therapeutic unfractionated heparin

Damian Ratano[a,*], Lorenzo Alberio[b], Frederik Delodder[a], Mohamed Faouzi[c], Mette M. Berger[a]

[a] Service of Intensive Care and Burn Unit, Lausanne University Hospital (CHUV) and Faculty of Biology & Medicine, University of Lausanne, Lausanne, Switzerland
[b] Division of Haematology and Central Haematology Laboratory, Lausanne University Hospital (CHUV) and Faculty of Biology & Medicine, University of Lausanne, Lausanne, Switzerland
[c] Institute of Social and Preventive Medicine (IUMSP), Faculty of Biology & Medicine, University of Lausanne, Lausanne, Switzerland

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ABSTRACT

Background: No study supports the use of either aPTT or anti-Xa activity for heparin monitoring in critical care patients. There are no strong data on the agreement between aPTT and anti-Xa. The aims of this study were to: 1. Analyse the agreement between aPTT and anti-Xa in a large population of critically ill patients under unfractionated heparin therapy (UFH), 2. Identify clinical and biological factors associated to agreement or disagreement, and 3. Analyse the impact of anti-Xa availability on the use of aPTT and UFH therapy.

Methods: Retrospective study in a 35 beds mixed-ICU population between 2006 and 2016 in a University teaching hospital. Inclusion criteria: delivery of a UFH dose > 15,000 U/24 h during at least one day with one anti-Xa determination. *Data*: demographic variables, aPTT, anti-Xa, laboratory variables, presence of extracorporeal devices (ECD). Pairs of simultaneously dosed aPTT and anti-Xa [aPTT:anti-Xa] were analysed on the basis of their agreement within the sub-therapeutic, therapeutic (aPTT 50–80″, anti-Xa 0.3–0.7 U/ml) or supra-therapeutic ranges.

Results: 2283 patient admissions (2085 patients) were analysed. 35,595 [aPTT:anti-Xa] pairs were found. The overall [aPTT:anti-Xa] agreement was 59.6% and lowest (54.3%) in presence of ECD compared to non-ECD patients (61.6%; $p < 0.001$). Sixteen demographic and biological variables were analysed and were not predictive of [aPTT:anti-Xa] agreement. No significant difference in administered UFH dose was observed after anti-Xa introduction.

Conclusion: In this large cohort, the [aPTT:anti-Xa] agreement is < 60% and significantly lower in patients with ECD. None of the variables identified as potentially affecting the agreement were predictive. Availability of anti-Xa had neither effect on aPTT use nor on UFH-dose. These results call for a prospective study to determine the optimal UFH-therapy monitoring tool.

1. Introduction

Anticoagulation with unfractionated heparin (UFH) is a mainstay in the critical care setting. An estimated 10–20% of intensive care unit (ICU) patients need therapeutic anticoagulation and probably many more in some specialised ICUs [1]. Even if UFH is a problematic medication, particularly because of the risk of developing heparin-induced thrombocytopenia [2], it is currently the only drug to have a relatively short half-life and a specific antidote and thus, to fulfil the needs of critical care medicine for therapeutic anticoagulation.

Monitoring the effect of UFH is a major problem. Since 1972 [3], aPTT is standard for UFH monitoring. The usually cited therapeutic range, corresponding to 1.5–2.5 of the baseline aPTT, defined by Basu et al. [3] is still widely used despite the poor scientific evidence of its effectiveness [4]. The aPTT measure is also highly variable due to technical biases [5,6]. This lack of consistency in the results of aPTT has led to the search for a new standard for UFH monitoring. Since the 90s, anti-Xa activity (hereafter anti-Xa) has progressively established itself

Abbreviations: anti-Xa, anti-Xa activity; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CAD, circulatory assisting device; CRRT, continuous renal replacement therapy; ECD, extracorporeal devices; ELSO, extracorporeal life support organisation; LDH, lactate dehydrogenase; UFH, unfractionated heparin

* Corresponding author at: Lausanne University Hospital (CHUV), Service of Intensive Care and Burn Unit, Rue du Bugnon 46, 1011 Lausanne, Switzerland.
E-mail addresses: Damian.Ratano@chuv.ch (D. Ratano), Lorenzo.Alberio@chuv.ch (L. Alberio), Mohamed.Faouzi@chuv.ch (M. Faouzi), Mette.Berger@chuv.ch (M.M. Berger).

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as an alternative for UFH monitoring especially in patients with heparin resistance [7]. Anti-Xa is a measure of heparin concentration and as such should be reproducible and more stable than aPTT which is an in vitro test assessing the delay of coagulation and intrinsically dependent on other variables [8]. Anti-Xa is even used for the calibration of the aPTT range in some laboratories [9,10]. The problem with this calibration is that the therapeutic range of anti-Xa is wide, is not clinically validated and varies between laboratories [7,11]. To the best of our knowledge there is no randomized controlled study to prove either the efficacy of anti-Xa or that of aPTT therapeutic range for UFH monitoring [12].

This has led to the current recommendation of the American College of Chest Physicians (ACCP) [4] that "*…more research is needed to identify the optimal approach for (…) UFH monitoring*." A few studies, with a small number of patients, most of which were not in an ICU setting, have been published and show poor [aPTT:anti-Xa] agreement [13–16].

Considering this, the clinician must choose between a well-known, old, inexpensive and rather variable method, and a new, more expensive and theoretically more reliable method. Since its introduction in 2006 in our ICU, UFH monitoring based on anti-Xa level has been debated both because of observed disagreement with aPTT and higher analytical costs.

The first objective of this study was to describe the proportion of agreement, in terms of therapeutic range, between anti-Xa and aPTT in a large mixed critical care population and in subgroups of patients with extracorporeal devices (ECD). The second objective was to identify clinical and biological factors associated with an agreement (or disagreement) between anti-Xa and aPTT. We also explored the influence of anti-Xa availability on the prescribed dose of heparin and on the use of aPTT.

2. Materials and methods

The study was conducted with institutional Ethics approval (Commission Cantonale de la Recherche Clinique N°2016–00789) on coded data, and individual consent was waived.

The ICU's patient database was screened (Metavision®) from 1.1.2006 to 31.12.2016. Inclusion criteria were age over 16 years, an effectively delivered dose of UFH > 15,000 U/24 h and at least one determination of anti-Xa. A cut-off of 15,001 units/day was used to define intended therapeutic anticoagulation. For every admission corresponding to the inclusion criteria we extracted demographic data, ICU length of stay, SAPS2 score, vital status at ICU and hospital discharge, laboratory and demographic variables associated with an alteration of aPTT and/or anti-Xa in previous studies [8] and the use of extracorporeal devices (ECD). The ECD included circulatory assisting devices (CAD; including intra-aortic balloon pump, extracorporeal membrane oxygenation and left and right ventricular assisting devices) and continuous renal replacement therapy (CRRT). Laboratory and demographic variables included in the analysis were, thrombin time, prothrombin time, fibrinogen, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total bilirubin, albumin, haemoglobin, leucocytes, C-reactive protein, procalcitonin, creatinine, age and body mass index. Every aPTT and anti-Xa was analysed on the same blood sample and at the same time, forming a pair (hereafter [aPTT:anti-Xa]. Every [aPTT:anti-Xa] was then analysed and classified according to its agreement with the subtherapeutic, therapeutic (aPTT 50–80 s; anti-Xa 0.3–0.7 IU/ml) and supra-therapeutic range. The therapeutic range for anti-Xa is the usual range defined in the literature and applied in our institution. To define the therapeutic range for aPTT our laboratory uses an in vitro spiking assay as internationally recommended [9].The pairs were first classified in 9 subgroups (Table 1) They were then pooled in 3 groups following the aPTT/anti-Xa range relationship (aPTT = anti-Xa; aPTT > anti-Xa; aPTT < anti-Xa). The dose of UFH delivered while attempting to anticoagulate the patients was extracted from the database. Laboratory variables used in the analysis of association with [aPTT:anti-Xa] were included only if they were sampled within a ± 3 h time interval around a [aPTT:anti-Xa]. We assumed that during such a short period, none would change significantly, hence permitting an accurate analysis of association with the related [aPTT:anti-Xa].

2.1. Laboratory assays

aPTT was determined with the reagents Dade Actin FA until noon of August 26th 2010, and Pathromtin SL afterwards. The employed coagulometers were a Sysmex CA-7000 until June 2013 and a Sysmex CS-5100 (Siemens Healthineers Global) afterwards. Anti-Xa activity was assessed by a chromogenic method (Biophen Heparin 6, Hyphen BioMed, Neuville-sur-Oise, France) calibrated with UFH standards.

2.2. Statistics

Summary data for continuous variables are reported as mean and standard deviation (SD) or medians and interquartile ranges (IQRs) as indicated. Categorical variables are reported as frequencies and percentage. Power discrimination of laboratory and demographic variables between concordant pairs (aPTT = anti-Xa) and non-concordant pairs (aPTT ≠ anti-Xa) were examined using logistic regression model (concordant pairs coded by 1 and not concordant pairs by 0). The data were clustered by patients. That is, the observations are independent across patients but not necessarily within patients. To account for the dependence within patients in estimating the variance-covariance matrix, we used a robust clustered sandwich estimator of variance to fit the model. For each continuous variable, fractional polynomial models were used to analyse the functional form with the outcome, and area under ROC-curve (AUC) was calculated. Stata/MP (version 14.2; StataCorp LP, College Station, TX, USA) was used for data processing and analyses.

3. Results

Out of 23,334 admissions during the 11 years' period 2319 (9.9%) admissions met the inclusion criteria enabling the analysis of 2283 (98.4%) admissions: 18 were excluded because of a short stay (< 24 h) and 8 were excluded because of an extremely long stay (> 250 days): please see flow chart in Additional file 1, Fig.S1. Patient population is described in Table 2.

Altogether, 68,841 anticoagulation tests were available (aPTT 68,660; anti-Xa 35,775) of which 35,595 [aPTT:anti-Xa] were analysed. The global [aPTT:anti-Xa] agreement in our cohort was 59.6%. The 40.4% of pairs with disagreement were characterized by an aPTT > anti-Xa in 30% and an aPTT < anti-Xa in 10.4% (Fig. 1). The κ coefficient was 0.472 (± 0.004) $p < 0.001$, reflecting a moderate correlation. The results of the subgroups according to the presence (CAD//CRRT) and/or absence (non CAD//non CRRT) of ECD showed a progressive decrease of [aPTT:anti-Xa] agreement when implementing ECDs. There was a statistically significant increase in the proportion of pairs with an aPTT > anti-Xa (from 25.6% to 38.3%; $p < 0.001$) and a simultaneous decrease of the aPTT = anti-Xa pairs (61.6% to 54.3%; $p < 0.001$) as well as of the aPTT < anti-Xa pairs (12.9% to 7.4; $p < 0.001$) (Fig. 1). The differences were linked to the type of device and the cumulative effect of every device.

The analysis of the impact of selected demographic and laboratory variables on [aPTT:anti-Xa] agreement did not reveal any significant association. None of the studied variables were predictive of the [aPTT:anti-Xa] agreement. The receiver operating characteristic (ROC) curves for the probability of agreement show low area under curve (AUC) with a minimum of 0.49 for creatinine and a maximum of 0.64 for thrombin time. ROC-curves for every analysed variable are available in the Additional file 1, Figs. S2 and S3.

The mean dose of UFH delivered in the ECD group (771 admissions)

Table 1
Pairs classification following the aPTT/anti-Xa relationship.

Anti-Xa range (IU/ml)	aPTT range (seconds) <50	50-80*	>80
<0.3	Agreement	Disagreement **aPTT>anti-Xa**	Disagreement **aPTT>anti-Xa**
0.3-0.7#	Disagreement **aPTT<anti-Xa**	Agreement	Disagreement **aPTT>anti-Xa**
>0.7	Disagreement **aPTT<anti-Xa**	Disagreement **aPTT<anti-Xa**	Agreement

*aPTT therapeutic range; # anti-Xa therapeutic range.

Table 2
Description of the 2283 admissions (2085 patients).

	N or mean	%/SD
Demographics		
Age (y)	63.7	14.7
Gender, male	1614	70.7
BMI (kg/m2)	26.9	6.0
SAPS2 score (pts) (on 2179 admissions)	47.3	17.6
Mechanical ventilation	1662	72.8
Diagnostic group		
Medical/surgical (on 1591 admissions)	949/642	60/40
Cardiovascular	1247	54.6
Sepsis	258	11.3
Respiratory	218	9.6
Bronchopneumonia	194	8.5
Neurologic	83	3.6
Digestive	81	3.6
Metabolism	49	2.2
Burn and trauma	78	3.4
Other	75	3.3
Specific treatment		
CRRT	533	23.4
CAD	346	15.2
CRRT and CAD	108	4.7
Outcome		
ICU los (days)	14.6	18.3
ICU non-survivor	297	13.0
Hospital non-survivor	432	20.7

Data expressed as number (%) and mean (± SD). BMI: body mass index; SAPS2 score: Simplified acute physiology score in points; CRRT: continuous renal replacement therapy; CAD: circulatory assisting devices including intraaortic balloon pump (IABP), left ventricular assisting devices (LVAD), right ventricular assisting devices (RVAD) and extracorporeal membrane oxygenation either veno-venous (VV-ECMO) or veno-arterial (VA-ECMO); ICU los: ICU length of stay.

did not change from 2006 to 2016 (Fig. 2).

Meanwhile, anti-Xa measurements increased massively, especially since 2009. The proportion of anticoagulated patients having a determination of anti-Xa level rose from 9.2% (2006) to > 99.7% (since 2014). 99.5% of anti-Xa assays was paired with aPTT testing. The mean number of aPTT per patient did not vary between 2006 and 2016. In contrast, the use of anti-Xa increased ten-fold over the same period (Fig. 3).

4. Discussion

The present study is, to date, the largest on the monitoring of UFH therapy in critical care patients. The most important finding is the low overall [aPTT:anti-Xa] agreement, which is < 60% (Fig. 1). Our data confirm the results of previous studies which, including smaller numbers of patients, indicated a 40–63% agreement [7,13–16]. Of note, the majority of previous data comes from non-ICU settings. In patients treated with CRRT and/or CAD, the [aPTT:anti-Xa] agreement progressively decreased to 54.3% (Fig. 1). This lower agreement when using ECD is cumulative and more significant with CRRT than with CAD. It is balanced by a rise in the aPTT > anti-Xa disagreement group. This indicates that when ECD are used, aPTT is higher in comparison to anti-Xa. This relation can be explained, from a patho-physiological point of view, by an activation of the contact phase with depletion of factor XII due to the presence of extra-corporeal surfaces [17,18]. To the best of our knowledge, these results are the first that point to this possible relationship. The patients with ECD require a well-conducted anticoagulation and therefore could benefit from the laboratory test least affected by the activation of the contact phase, hence anti-Xa.

The anti-Xa and particularly the aPTT are laboratory assays submitted to pre-analytical, analytical and biological constraints that may alter their result. We selected only [aPTT: anti-Xa] pairs dosed on a same blood sample to minimize pre-analytical bias. The analytical conditions are standardised in a single center and an institutional process guarantees the quality of analysis. Takemoto et al. [19] attempted to explain the [aPTT:anti-Xa] discordance and identified that factor II and VIII might play a role. This is certainly true, but these coagulation factors are not routinely available and generate costs. Moreover, due to the paucity of data, we could not analyse their impact on [aPTT:anti-Xa] agreement. We then decided to integrate the factors identified by Vandiver et al. [8] into our query. These factors (inflammation, infection, impaired kidney function, bilirubin, age, obesity and a few others) are not directly linked to coagulation, but are supposed to alter aPTT and/or anti-Xa results. Their concordance may thus increase or decrease. It is important to mention that most of the factors described by Vandiver et al. [8] are routinely obtained and do not generate any additional cost. Despite a very large dataset, a thorough statistical analysis indicated that none of the aforementioned variables were predictive of [aPTT:anti-Xa] agreement. The ROC-curves shown in the Additional file 1 have very low AUC, ruling out any ability of these variables to predict [aPTT:anti-Xa] agreement even by combining them. This highlights the fact that aPTT and anti-Xa are really testing different pathways, both being affected by multiple factors. This might justify randomized control trials, targeting clinical outcomes such as bleeding and thrombotic events, to determine which one of these two tests is more effective for UFH monitoring in different critical care patient populations.

One of the goals of this study was to observe the use of anti-Xa in our tertiary centre. Indeed, anti-Xa was introduced progressively in many hospitals, while the level of evidence to support its use remains low [4]. In our institution anti-Xa use started in year 2005–2006. Of note, anti-Xa is much more expensive than aPTT (aPTT 8€; anti-Xa 40€

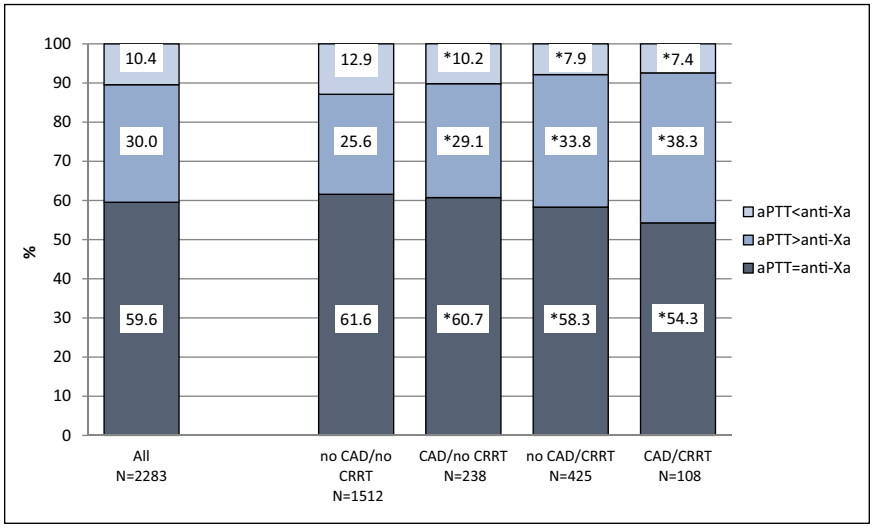

Fig. 1. Proportion of [aPTT:anti-Xa] agreement and disagreement in the cohort (All) and in the subgroups. CAD: circulatory assisting devices; no CAD: absence of CAD; CRRT: continuous renal replacement therapy; no CRRT: absence of CRRT; * $p < 0.001$.

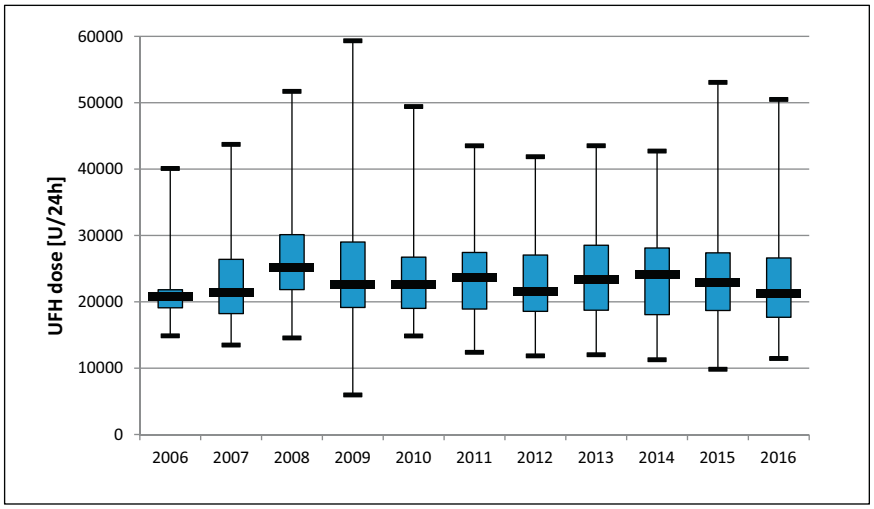

Fig. 2. Unfractionated heparin doses evolution over the years in patients with extracorporeal devices. Thick horizontal bars are median of the yearly mean dose. Boxes show interquartile ranges. Thin bars represent min and max values. UFH: unfractionated heparin.

at this institution). An industry sponsored study published in 1999 [20], including a small subset of non-ICU patients, concluded that monitoring UFH with anti-Xa, versus aPTT, represented a modest increase in costs that was outweighed by the other advantages of anti-Xa. In our population, we have estimated the cost of anti-Xa to be 1.65 million Swiss francs (1.45 million €) during the 11-year study period. The current economical limitations of most modern ICU and hospitals should not allow such financial expenditure without strong evidence of

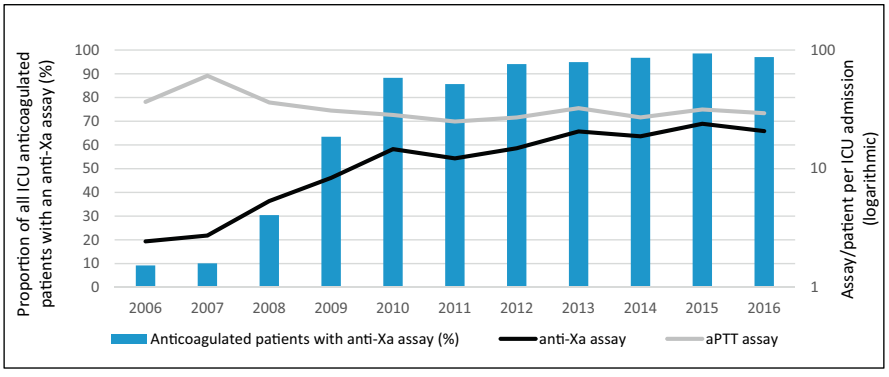

Fig. 3. Evolution of activated thromboplastin time and anti-Xa activity assay through years. Bars refer to the left axis. Continuous lines refer to the right axis. aPTT: activated partial thromboplastin time, anti-Xa: anti-Xa activity.

the benefits. As a final argument on the economic impact of anti-Xa, our data show that the increase in anti-Xa measurements was not balanced by a decrease in aPTT dosing (Fig. 3).

Another very compelling result was that 99.5% of anti-Xa assays were paired with aPTT. The exact reason for the systematic simultaneous dosing of anti-Xa with aPTT is unclear. Two hypotheses may explain this. First, the medical team, typical of a teaching hospital, is a mix of older and younger physicians. Senior physicians are probably used to aPTT because they have been using it for a long time. Junior physicians tend to use anti-Xa because it is more “modern”, they were taught to use it at medical school, and are familiar with its use when monitoring low-molecular-weight heparin. Second, the lack of strong evidence and the absence of international recommendations are a source of confusion and misuse of the laboratory tools. This leads to a situation where beliefs are stronger than scientific knowledge and evidence.

An objective of our study was also to verify the effect of anti-Xa use on UFH delivered dose. Levine et al. [7] studied the specific “heparin-resistant” population. One of their main results, justifying the spread of anti-Xa as a UFH monitoring method, was the reduction of delivered UFH when using anti-Xa and thus probably a lower risk of bleeding. Amongst the observations that inspired our study was the feeling of some senior physicians that UFH doses had increased significantly in recent years, perhaps due to the use of anti-Xa. We explored this hypothesis. In the absence of recommendation to use either aPTT or anti-Xa in our ICU, we hypothesised that the increased use of anti-Xa assay (Fig. 3) over the years was linked to the adherence of clinicians to anti-Xa results. The consequence should have been a decrease in the mean delivered UFH dose. This particular aspect could only be studied in the ECD group (771 patients) showing the highest discordance of [aPTT:anti-Xa] (Fig. 2). No change in the dose of delivered UFH could be found. Our result neither confirms the suspicion of an increasing dose of heparin due to the anti-Xa use, nor Levine et al.'s result of a dose reduction. This discrepancy in findings is possibly explained by the wide therapeutic window of UFH.

Searching for a rational way to monitor UFH treatment, the present data do not provide an argument in favour of either assay. These data reflect well the current state of knowledge. A recently published international survey on ECMO anticoagulation technique [21] shows a wide variability in the use of UFH monitoring around the world. The authors conclude that the lack of standard practice probably reflects the lack of data for optimal anticoagulation in ECMO patients and highlights the current situation in which every individual hospital has its own way of monitoring UFH. This is emphasized by some international recommendations such as that of the Extracorporeal life support organisation (ELSO) [22] stating that every ECLS program has to find an institutional approach to monitor UFH. Prospective studies assessing UFH concentration, impact on in vivo thrombin generation and – at best – clinical outcomes are needed.

4.1. Study limitations

Due to its retrospective and monocentric design, this study has clear limitations, including that of external validity. Nevertheless, the large quantity of data and the few missing data of our patient database ensure good data quality. As the behaviour of our physicians was not an endpoint of the study, the retrospective design did not enable any conclusion as to their impact on laboratory determinations. However, the link between the [aPTT:anti-Xa] result and the subsequent handling of UFH dose would be a very interesting approach to explain how physicians manage the situation in real time and how they integrate their knowledge, the patient situation and the laboratory data. Owing to administrative changes during the study period, we also deplore the absence of data regarding complications of anticoagulation: a change in their incidence might have provided answers as to the optimal assay.

5. Conclusion

At least 15% of our ICU patients receive UFH and this drug remains a key treatment for most ECD. This study shows that the agreement between aPTT and anti-Xa is low, particularly in the latter population. Moreover, we could not find any variable beside ECD that was predictive of [aPTT:anti-Xa] agreement and the evidence for the use of these laboratory tests is weak. Due to the large use of low molecular weight heparins and newer anticoagulant drugs out of the ICU, UFH therapy has become an almost characteristic feature of critical care. As the last frequent users of UFH, critical care specialists have to conduct well-designed and randomized studies to define the best monitoring tool for UFH in ICU patients.

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Availability of data and material

Data are available on reasonable request from the corresponding author but prior approval by the Institutional Ethics Commission is mandatory.

Authors' contributions

DR and MB were responsible for all aspects of the study. LA was responsible for scientific supervision of hematologic aspects, interpretation of results and manuscript preparation. FD was responsible for data preparation, data interpretation and statistical analysis. MF was responsible for statistical analysis. All authors approved the manuscript.

Declaration of interests

None.

Meeting presentation

The preliminary results were presented in 2017 at the European Society of Intensive Care Medicine (ESICM) meeting in Vienna (Austria) and at the Swiss ICU meeting in St-Gall (Switzerland).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.01.002.

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