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Letter to the Editors-in-Chief

Limitations on point care APTT for monitoring of unfractionated heparin in intensive care patients

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In our previous study entitled “Should we abandon the APTT for monitoring unfractionated heparin?”, we have highlighted the limitation of standard (laboratory) activated partial thromboplastin time (APTT) in monitoring of unfractionated heparin (UFH) (1). It was demonstrated that discordance of APTT and anti-Xa level in adults and children may be due to elevated fibrinogen levels [1]. In this present study, we are extending the literature to provide more evidence regarding the limitations of the use of point of care testing (POCT) APTT in monitoring UFH in critically unwell intensive care patients. POCT is a growing field that provides easy and quick access to required results at the bedside or at least closer to the patient than standard laboratory tests. POCT devices for monitoring of prothrombin time (PT)/ international normalized ratio (INR) are well established and have made the anticoagulant monitoring of vitamin K antagonists (VKAs) easier for patients and anticoagulant clinics. The APTT is a similarly cheap and readily available test that is commonly used for monitoring UFH, but there is no equivalent POCT method for the purpose of monitoring the APTT as there is for the INR, and there is also a lack of international standardisation of APTT testing, which again is different from the PT/ INR. Therefore, the APTT therapeutic range must be established individually for each laboratory. Based on comparisons using an anti-–factor Xa chromogenic assay to measure UFH, in 50 patients on a stable UFH infusion as an anticoagulant, with the APTT within our hospital, we found an APTT of 60–100 s corresponds to the recommended anti-Xa therapeutic range of 0.3 to 0.7 IU/mL [1]. However, it is our standard practice to maintain anti-Xa: 0.2–0.3 IU/mL which corresponds to APTT of APTT 50–60 s for patients receiving veno-venous (VV) extracorporeal membrane oxygenation (ECMO) and anti-Xa: 0.3–0.5 IU/mL which corresponds to APTT of APTT 60–80 s for patients receiving veno-arterial (VA) ECMO unless they have an indication to receive therapeutic anticoagulation with UFH such as acute thrombosis or mechanical heart valve. It is likely that the APTT relationship with heparin concentration is susceptible to confounding by variations in other coagulation factors, especially in patients in intensive care units who are acutely unwell with infection/inflammation. Consequently, it is our practice to use the anti-Xa level to monitor anticoagulation with UFH.

Although it has some practical and theoretical disadvantages, many centres use the APTT to monitor UFH. The PT POCT device requires only a small volume of blood (8 μL compared to 2.7 mL for a laboratory APTT), and a similar device for POCT APTT would be very appealing for clinicians especially in intensive care where frequent monitoring of APTT to adjust UFH dose is needed. CoaguChek® Pro II (Roche Diagnostics Limited) has been proposed for assessment of the APTT to determine coagulation factor deficiencies and for monitoring of UFH anticoagulation. Unlike POCT monitoring of PT/INR, POCT APTT to monitor heparin has not been widely adopted or trialled. This is partly because there is no equivalent standardisation for APTT as for PT/INR, but also due to the lack of a suitable device. The aim of this prospective single centre observational study was to assess whether the Coagucheck APTT (Roche APTT cassette & Coaguchek XS Pro meter) is comparable to a laboratory APTT and has a linear response to UFH over the therapeutic range. This was a prospective observational study and was undertaken as a service evaluation project and approved by the Trust clinical effectiveness unit.

APTT was tested simultaneously on the Coagucheck APTT and the Werfen ACL TOP500 analyser using SynthASil (HemosIL®, Werfen, Warrington, Cheshire, UK) in 80 adult patients (age $>$ 16 years) from an adult intensive care unit. Since this a tertiary referral centre ECMO, the majority of patients at any given time are receiving ECMO. POCT APTT was performed by a single operator to avoid inter-operator variability. Samples were tested within 3 min of collecting into a plain syringe and the first 4 drops were discarded before being applied to the test strips. Part of the sample from the plain syringe was added to tubes containing 0.109 M trisodium citrate in the proportion 9:1 (Vacutainer Plus, Becton Dickinson, Franklyn Lakes USA). This same sample was tested for laboratory APTT and used to measure heparin anti-Xa level using chromogenic a Liquid anti-Xa assay which does not use exogenous AT (Werfen, Warrington, Cheshire, UK). Each patient was tested only once.

Data analysis was performed using GraphPad Prism® version 8 (GraphPad Software, Inc. La Jolla, USA). Results were reported as median and range. Correlation was assessed for POCT APTT vs lab APTT, and for both APTTs with heparin anti-Xa, using Spearman's rank correlation. All statistical tests were 2 sided and significance was set at $p < 0.05$. As the data were non-normally distributed, linear regression was not performed. However, the relationship between laboratory APTT vs POCT APTT and anti-Xa is presented graphically.

Median (range)age of the study population was 54 (16–83) years and 60% were male. Although overall correlation between laboratory

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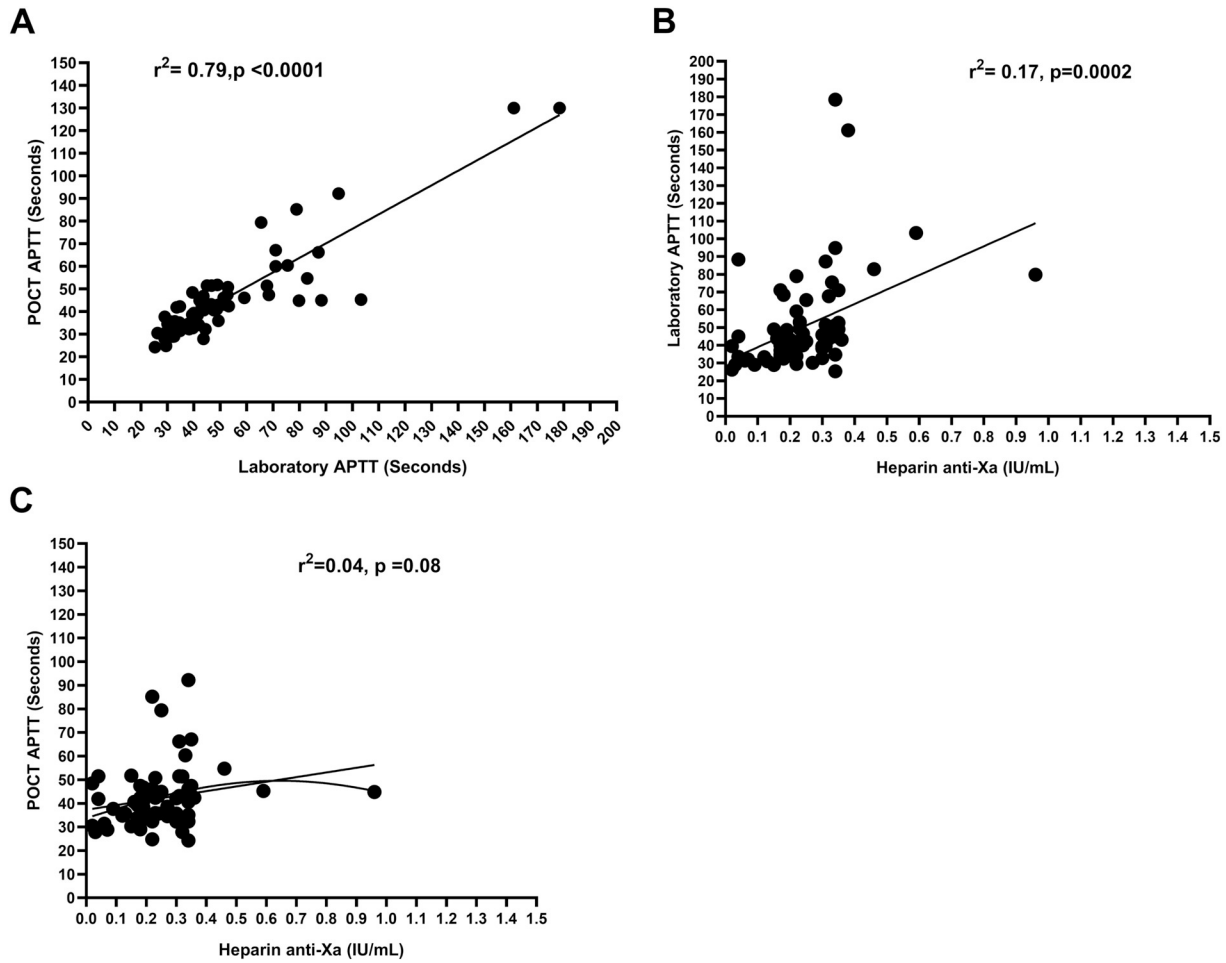

Fig. 1. A. Correlation between POCT APTT vs laboratory APTT, B. correlation between Heparin anti-Xa vs laboratory APTT, panel 1C. Correlation between Heparin anti-Xa vs POCT APTT.

APTT and POCT was good (r = 0.83, 95% confidence interval (CI), 0.73–0.89, p < 0.0001), this was only when the APTT was < 60 s (Fig. 1a). As previously reported for this group of patients, the correlation between heparin anti-Xa level and laboratory APTT was only moderate (r = 0.51, 95% CI, 0.31–0.67, p < 0.0001). We found that the correlation between heparin anti-Xa level and the POCT APTT was poor (r = 0.03, 95%CI 0.06 = 0.51, p = 0.01) (Fig. 1b and c).

This is the first study to report the lack of reliability in using POCT APTT in monitoring UFH in a prospective well-designed study in patients receiving UFH in critically unwell patients. In this study, there was a good correlation between laboratory APTT and POCT specifically when the APTT was < 60s. However, laboratory APTT showed only a moderate correlation, and POCT APTT showed a poor correlation, with heparin anti-Xa levels in critically unwell patients receiving UFH. The majority of patients (52/80, 65%) received UFH for VV-ECMO and heparin anti-Xa level was within the therapeutic range for this indication in 76% of the patients (anti-Xa of 0.2–0.3 IU/mL). However, laboratory APTT and POCT APTT were within the expected therapeutic range in only 30% and 22% patients respectively. Of particular concern is the lack of APTT prolongation in the POCT APTT once the heparin anti-X level rises above 0.4 IU/mL.

The standardisation of monitoring UFH using the APTT between laboratories has not been achieved because of the considerable reagent and instrument variability leading to inconsistency in sensitivity to heparin [2–4]. APTT reagents from different manufacturers, and even different batches, show considerable and clinically important variation when heparin concentration by protamine assay is compared with APTT ratio [5].

Based on this study, neither POCT APTT nor laboratory APTT is a suitable option for monitoring UFH in critically unwell intensive care patients. Lack of reliability of laboratory APTT in monitoring UFH is in keeping with our previous studies [1] and we extend the findings to limitations on use of POCT APTT in monitoring UFH in critically unwell patients. Although a POCT device does not necessarily need to provide correlation with APTT and heparin anti-Xa levels, it may be used to generate discrete variables such as to identify patients are under-anticoagulated, within range and over anticoagulated. However, based on our study data, even this cannot be reliably concluded. As there is a good correlation with laboratory APTT and POCT APTT especially where results are < 60s, POCT APTT may be an option for screening for coagulation factor deficiency/coagulopathy or monitor UFH in stable patients without acute infection/inflammation. However, this needs further investigation.

Author contributions

DRJA was involved in the study concept, design, analysis, interpretation of data, and preparation of the first draft of the manuscript. ML was involved interpretation of the data and revising the manuscript. LV was involved in performing the POCT APTT, data collection and revising the manuscript. All authors approved the final manuscript.

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Declaration of competing interest

Authors state that they have no relevant conflict of interest.

References

[1] D.R.J. Arachchillage, F. Kamani, S. Deplano, W. Banya, M. Laffan, Should we abandon the APTT for monitoring unfractionated heparin? Thromb Res 157 (2017) 157–161.
[2] R.A. Marlar, J.N. Gausman, The effect of instrumentation and laboratory site on the accuracy of the APTT-based heparin therapeutic range, Int J Lab Hematol 34 (2012) 614–620.
[3] E.J. Favaloro, R. Bonar, J. Sioufi, M. Wheeler, J. Low, M. Aboud, et al., An international survey of current practice in the laboratory assessment of anticoagulant therapy with heparin, Pathology 37 (2005) 234–238.
[4] M.L. Brigden, M. Johnston, A survey of aPTT reporting in Canadian medical laboratories. The need for increased standardization. Thrombosis Interest Group of Canada, Am J Clin Pathol 114 (2) (2000) 276–282.
[5] P. Brill-Edwards, J.S. Ginsberg, M. Johnston, J. Hirsh, Establishing a therapeutic range for heparin therapy, Ann Intern Med 15 (119) (1993) 104–109.

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