Resistance or pitfall in heparin monitoring: An ongoing issue in COVID-19 anticoagulation

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LETTER TO THE EDITOR

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Dear Editor,

We read with great interest the recent article by Novelli and colleagues describing the presence of heparin resistance in COVID-19 patients in the intensive care unit (ICU).[1] Current evidence demonstrates that COVID-19 patients are at high risk for thrombosis, even those receiving standard or intensified thromboprophylaxis doses with low molecular weight heparin (LMWH) or unfractionated heparin (UFH).[2] Novelli et al.[1] mentioned that about 75.7% of patients (28/37 patients) receiving UFH/LMWH might be considered as heparin resistant, and 51.3% experienced thromboembolic events, suggesting prophylactic heparin insufficiently downregulates coagulation.

In the intensive care unit (ICU), heparin resistance is expected, particularly in critically ill patients with more severe systemic inflammation. A previous study by White et al. also demonstrated failure to achieve therapeutic anticoagulation levels as measured by APTT or anti-Xa assays in COVID-19 ICU patients. They showed that resistance to therapeutic UFH occurred in 8 out of 10 patients and that peak anti-Xa peaks were suboptimal in 5 out of 7 patients receiving therapeutic LMWH.[3] Novelli et al.[1] and White et al.[3] have offered some possible insights into why the high failure rate of thromboprophylaxis is seen in COVID-19 when standard thromboprophylactic doses are used.[4]

Heparin resistance is generally defined as high doses of UFH greater than 35 000 IU/day required to achieve anticoagulation.[5,6] A weight-based definition of resistance (IU/kg/hr) may be more appropriate; however, the consensus is lacking. A study by Weeks et al. defined resistance as requiring ≥21 IU/kg/hr of heparin.[7] Because similar criteria were also lacking for LMWH, Novelli et al. have arbitrarily defined LMWH resistance as not achieving the expected anti-Xa range.[1] Heparin resistance is a concern when a hefty dose of heparin is required to elicit a subtherapeutic or inadequate response. In this condition, the question of true resistance versus pseudo-resistance becomes relevant to be discussed. Identifying heparin resistance can be challenging to physicians, primarily because of its common use in acute or intensive care settings.

In COVID-19, acquired AT deficiency is rare but can occur in some patients, even those not critically ill.[8] Novelli et al. showed that all patients had mean AT levels 83±17% (reference range: 80%–120%), and no AT supplements were administered.[1] High levels of heparin-binding proteins associated with acute-phase reactions tend to be typical in COVID-19 patients.[8] COVID-19 patients also have high FVIII and FIB, artificially lowering the APTT level, so some pseudo-resistance might be expected.[3,9] In vitro studies using blood from COVID-19 patients showed that the addition of heparin resulted in lower than expected anti-Xa activity.[3] This supports the presence of low heparin concentration due to acute-phase proteins. Increased UFH clearance associated with the inflammatory state again confirms the resistance.

Two different strategies are commonly used to monitor the therapeutic effects of UFH: APTT and anti-Xa assay. APTT is usually performed for UFH monitoring because it is a widely available and inexpensive parameter. Despite that, the laboratory method used in evaluating the APTT greatly influences the therapeutic range because of the significant reagent-to-reagent variability.[10] Several guidelines recommend that each institution define its own APTT therapeutic range (corresponding to 0.3–0.7 IU/ml anti-Xa) used in the laboratory rather than a usual fixed APTT therapeutic range 1.5–2.5 times control.[10] APTT can also be affected by increased FVIII or FIB levels, causing pseudo heparin resistance. Conversely, monitoring heparin using anti-Xa takes advantage of a narrower reagent variability and was not affected by FVIII or FIB.[10,11] The overall superiority of anti-Xa over APTT in monitoring heparin therapy is controversial; however, the current evidence signifies better anti-Xa reliability for clinical monitoring of critically ill patients.[11] Lawlor et al. showed APTT potentially underestimate heparin activity in COVID-19 patients receiving UFH compared with anti-Xa, and APTT alone may be an unreliable measure of heparin activity.[12] In addition, anti-Xa assay is a reliable determinant of blood LMWH concentrations, especially in particular populations, such as severe obesity or renal failure patients, where dose-finding studies have not been carried out.[10]

Consistent with previous results, Novelli et al. demonstrated anti-Xa was a more potentially reliable method in heparin monitoring than APTT in acute COVID-19 patients. Anti-Xa was insensitive to increase levels of FIB, FVIII, and Lupus anticoagulant (LAC) that are common during inflammatory state of COVID-19.[1] Nevertheless, Lisman et al. have previously shown that in liver disease, patients, who frequently have AT deficiency, anti-Xa, and APTT, are not suited for estimating heparin concentrations. While the anti-Xa vastly underestimates heparin levels, the thrombin generation test shows that heparins effectively downregulate coagulation.[8] Based on these limited COVID-19 data, we agree with Novelli et al. to suggest monitoring the heparin activity based on anti-Xa with a target value of 0.3–0.7 IU/ml in all COVID-19 patients, instead of based on APTT levels; and specifically add thrombin generation test in patients with liver disorder.

If the APTT is low and heparin resistance is suspected, a cofactor AT-heparin test is recommended to confirm AT deficiency.[5] Most laboratories set the lower limit of normal for AT activity at approximately

80%–120%. The supplementation of antithrombin to the anti-Xa assay may avoid potential interferences, and it has been demonstrated that assays supplemented in this way have improved heparin recovery, especially when the levels of AT have dropped below 40%.[13]

High-dose UFH may be received by critical COVID-19 patients, such as for extracorporeal membrane oxygenation (ECMO) or hemodialysis, where activated clotting time (ACT) can be a monitoring option. In these settings, the APTT and anti-Xa may not be helpful because the doses of heparin administered often result in a plasma heparin concentration >1 IU/ml, exceeding APTT and anti-Xa analytical range limits,[14] which can be stretched by expanding the calibration.[15] Rhoades et al. stated that anti-Xa proved to be associated with greater likelihood of achieving therapeutic values, fewer UFH titrations, and a trend toward lower UFH doses.[16] Several contrasting studies showed that ACT value was poorly correlated with anti-Xa and did not correlate with UFH dose in patients undergoing ECMO.[17] We still recommend using ACT as a rapid bedside test for monitoring high dose UFH since the ACT shows a dose-response to heparin concentrations in the range of 1–5 IU/ml.[14]

In conclusion, identifying clinical heparin resistance in COVID-19 may become a challenge for physicians, especially in the ICU setting. When clinical resistance is suspected, physicians must ensure sufficient heparin activity in the patient, ideally by checking anti-Xa and activated prothrombin time ratio (APR). APR is a modification of the APTT result: the patient's APTT divided by the mean of the normal range. APR has unique advantages in that it reflects the hypercoagulable state and the particular importance of the contact activation inhibition, which is not reflected in the anti-Xa assay.[18] A clinical decision must be made whether there is a risk of excessive bleeding and whether a dose increase is recommended. Proper modalities in heparin monitoring can define the desired therapeutic anticoagulation level.

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activated partial thromboplastin time, anti-Xa, COVID-19, heparin, intensive care, resistance

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M.Y.A. and E.P.B.M conceived the idea, designed, and drafted the work, revising critically for important intellectual content. All authors revised and approved the version to be published.

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Not applicable.

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Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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