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Letter to the Editor

Anticoagulation in COVID-19 patients requiring continuous renal replacement therapy

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Dear editor,

Ever since December 2019, the number of patients with SARS-CoV-2 infection continues to increase [1]. The incidence of acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) in critically ill patients with severe SARS-CoV-2 infection is significant [2]. The requirement of continuous renal replacement therapy (CRRT) varies according to various risk factors such as admission to the intensive care unit (ICU), requirement of vasopressors and mechanical ventilation. Patients with stage-3 AKI usually need support with CRRT [2]. Various studies have shown that patients with SARS-CoV-2 infection are at an increased risk of systemic thrombosis due to hypercoagulable state, as suggested by the elevated D-dimer, Von Willebrand Factor antigen activity and factor VIII activity [3]. One theory proposed that the complete lack of clot lysis might contribute to thromboembolic events in this population, especially if accompanied with acute kidney failure [4]. Hypercoagulability could enhance clotting of the CRRT filter and compromise the CRRT efficiency [5]. Hence, anticoagulation is essential to maintain the patency of the extracorporeal circuit [5]. Data describing clotting and anticoagulation in patients with SARS-CoV-2 requiring CRRT are scarce... We sought to describe our experience where we needed to use higher doses than usual of anticoagulation therapy in this population.

This is a retrospective analysis of the CRRT filter clotting and the newly implemented anticoagulation protocols in patients with confirmed SARS-CoV-2 infection admitted to the ICU and received CRRT at our quaternary care hospital. Data collection was commenced after we received the Research Ethics Committee approval. All consecutive adults admitted to the ICU during the 3 study periods were enrolled.

Our CRRT anticoagulation before the pandemic relied mainly on using circuit heparin. The starting dose was 250–500 units/hour of IV heparin without a bolus and the dose was titrated upwards up to 1000 units/hour depending on transmembrane pressure, filter clotting, and also post filter aPTT. The post filter aPTT was checked on daily basis through the peripheral venous blood and the target aPTT range was 40–60 s. The pre filter replacement percentage is typically 50–100%. Regional citrate was rarely used.

The number of patients with COVID-19 infection admitted to the ICU started increasing in our hospital since late March 2020. We noticed a significant reduction in optimal CRRT filter's half-life secondary to frequent clotting. At the same time, published reports showed a higher incidence of clotting in this population [3,4]. Hence, we revised the current CRRT anticoagulation protocol and optimised it by recommending the use of systemic intravenous (IV) heparin with activated PTT (aPTT) goal of 60–85 aiming to: lower the incidence of CRRT circuit clotting, reduce the frequent interruption of the CRRT, and prolong the filter half-life. This protocol was approved by the nephrology and the critical care teams. Additionally, prior to initiation of the systemic IV heparin, a bolus dose of 1000 units of heparin infused to the circuit, followed by continuous heparin in CRRT circuit at 1000–1250 units per hour. If the circuit clots more than once prematurely then this patient becomes eligible for the new systemic IV heparin protocol.

We compared the CRRT filter's life over 3 periods of time to investigate the efficiency of the new protocol. The first period was from the 1st of January 2020 until the 29th of February 2020, prior to the pandemic, during which we were using the standard protocol (described earlier) and we did not have any proven COVID-19 patients in the ICU. The second period was between the 1st of April 2020 and the 8th of May 2020, during which we were using the standard protocol with patients infected by SARS-CoV-2. The third period was between the 9th of May 2020 and the 10th of June 2020, where we implemented the new systemic IV heparin protocol in critically ill with SARS-CoV-2 infection.

During the first period, 536 CRRT treatment days were completed for 67 patients (on average 9 patients treated with CRRT daily). Mean filter life was 46 ± 10 h (Median: 45 h, interquartile range (IQR): 39–51), the mean circuit heparin dose was 500 ± 125 units per hour with no bolus, and the mean post filter aPTT was 42 ± 3 s. During the second period, 489 CRRT treatment days were completed for 23 patients (on average 13 patients treated with CRRT daily). The mean filter life significantly dropped to 16 ± 6 h (median: 15.5 h, IQR: 12–20), the mean circuit heparin dose was 500 ± 188 units per hour with no bolus and the mean post filter aPTT was 46 ± 4 s. During the third period (the systemic IV heparin phase), 459 CRRT treatment days were completed for 24 patients (on average 14 patients were treated with CRRT daily). Mean filter life increased to 41 ± 6 h (median: 42 h, IQR: 37–47); 72% of treatment days were completed with circuit heparin mean dose of 1250 ± 125 units per hour after a bolus dose of 1000 units, and a mean post filter aPTT 68 ± 4 s; 23% of treatment days were performed with systemic IV heparin (mean dose 1200 ± 160 units/hour) with mean post filter aPTT of 72 ± 5 s. Table 1 describes the patients' demographics and filter life in the 3 periods. Kruskal–Wallis test was used to assess statistical significance between medians. The median filter life of

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Table 1

Period	Number of patients	Number of treatment days	AGE (years)	SEX	Diabetes (number of patients)	HTN (number of patients)	Mean filter life (hours)	Median filter l ife (hours)	IQR
1	67	536	60 ± 8	Males (67.1%)	60	65	46 ± 10	45	39–51
2	23	489	61 ± 7	Males (69.5%)	20	22	16 ± 6	15.5	11.5–19.5
3	24	459	63 ± 7	Males (66.6%)	21	22	41 ± 6	42	37–47

Period 1 was from the 1st of January 2020, till the 29th of February 2020; Period 2 extended from the 1st of April 2020, till the 8th of May 2020; Period 3 extended from the 9th of May 2020, till the 10th of June 2020. HTN: Hypertension, IQR: interquartile range.

period 1 was significantly higher than that of period 2 (p = 0.02), which was in turn significantly lower than the median filter life of period 3 (p = 0.01) (Table 1). The mean duration of CRRT per patient was 7 ± 2 days during period 1, 11 ± 1 days during period 2, and 9 ± 2 days during period 3.

As described earlier, with the adjustment of heparin and using the systemic IV heparin protocol significantly improved the filter life. However, we did not look at other thromboembolic events outside the dialysis filter. In the meantime, there was no major bleeding in those who received the new IV heparin protocol. Patients with severe SARS-CoV-2 infections can develop multi-organ failure and the coagulation profile could resemble the disseminated intravascular coagulopathy but usually presents with thrombosis and not bleeding [3,4]. Using aPTT to monitor anticoagulation with unfractionated heparin in any inflammatory state may not reflect the underlying anticoagulant activity. It may be skewed by the increased levels of factor VIII and fibrinogen and low levels of antithrombin. Using anti-Xa activity may reflect better picture of the coagulation state in this population. That was not done given the retrospective nature of the study [4].

In conclusion, higher dosing of circuit and/or intravenous heparin lowers the incidence of clotting and prolongs filter life during CRRT in patients with severe SARS-CoV-2 infections, which may improve patients' outcomes. Anti-Xa activity could better be used to monitor the anticoagulation state in this population rather than aPTT.

Compliance with ethical standards

The study was approved by the Clinical Research Ethics Committee of Cleveland Clinic Abu Dhabi and consent was waived due to the observational nature of the study.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy (patients' data) but are available from the corresponding author on reasonable request.

Authors' contributions

All 5 authors participated in the study design and reviewing of the patients' information and results. All 5 authors are responsible for the integrity of the data. NA, SG, and RM collected data. Data analysis was performed by NA, JM and WSE. NA, SG, and RM wrote the first draft of the manuscript. All authors contributed scientifically to the subsequent versions. All authors read and approved the final manuscript.

Disclosure of interest

The authors declare that they have no competing interests.

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