Submitted March 2021; Accepted January 2022

ORIGINAL ARTICLE

Frequent CRRT circuit failure in COVID-19: observations of a novel anticoagulation approach

H. de Lau[1], S.M. Kilian[2], M.S. Vink[2], G. Middelaar[2], A. Dooms[2], E.A. Vlot[1], A.J. Meinders[3]
Departments of [1]Anaesthesiology and Intensive Care, [2]Intensive Care and [3]Internal Medicine and Intensive Care, St Antonius Hospital, Nieuwegein, the Netherlands

Correspondence
H. de Lau - h.delau@gmail.com
ORCID ID: 0000-0002-2799-2914

Keywords - renal replacement therapy, COVID-19, anticoagulation, hypercoagulability, intensive care medicine, continuous venovenous haemofiltration

Abstract

Background: Continuous renal replacement therapy in the treatment of patients with active COVID-19 is frequently complicated by thrombosis in the extracorporeal circuit resulting in reduced filter lifespan, necessitating a revisited anticoagulation strategy.

Methods: The standard regional citrate anticoagulation dose of 2.2 mmol/l was increased to a starting dose of 3.0 mmol/l and routine thrombosis prophylaxis with low-molecular-weight heparin was adjusted from a single dose of nadroparin 2850 IU to 5700 IU twice daily. In a non-randomised cohort study, the efficacy of high-dose anticoagulation was compared with a control group with standard anticoagulation.

Results: Eleven COVID-19 patients requiring continuous renal replacement therapy were included, 42 filter sets in the control group and 37 filter sets in the high-dose anticoagulation group. The median filter lifespan was 48 hours in the high-dose anticoagulation compared with 18 hours in the control group ($p<0.001$). No significant effect on ionised calcium levels was observed in the high-dose group.

Conclusion: The combination of high-dose regional citrate anticoagulation and increased-dose LMWH appears to prolong filter lifespan in patients with COVID-19.

Introduction

While respiratory failure is central to the COVID-19 syndrome, renal impairment is a common complication with an estimated 20% of critically ill COVID-19 patients requiring renal replacement therapy.[1,2] Moreover, severe COVID-19 syndrome is frequently complicated with coagulopathy.[3,4] Although the pathophysiology is incompletely understood, a predominantly procoagulant pattern is observed with a combination of hypercoagulable state[5,6] and reduced fibrinolysis[7] and leads to a high cumulative incidence of thrombotic complications in critically ill COVID-19 patients.[8-10] The presumed coagulation abnormalities have also been associated with short continuous renal replacement therapy (CRRT) filter survival times due to frequent circuit thrombosis.[5,11,12] The overwhelming number of COVID-19 patients in combination with diminished CRRT circuit lifespan would not only have quickly led to shortages in materials but also to loss of red blood volume and inadequate CRRT. Regional citrate anticoagulation (RCA) can lengthen filter life and is associated with fewer bleeding complications than systemic heparin and is the standard anticoagulation modality in our centre.[13] In view of the frequent thrombotic complications and reduced CRRT filter life, the regional citrate and low-molecular-weight heparin (LMWH) dose were increased aiming to increase CRRT filter lifespan. In this observation cohort study, we report the median CRRT filter lifespan of the period before and after introduction of high-dose anticoagulation.

Methods

Study design and population

A single-centre cohort study was performed at the intensive care unit (ICU) of a large teaching hospital where approximately 2500 ICU patients are admitted on a yearly basis. Approval from the local Medical Ethics Committee was obtained with a waiver for patient informed consent due to the observational nature of the study (MEC-U; Research and Development Department St. Antonius Hospital, trial number w20.164). Data were collected retrospectively. Patients were eligible when CRRT was initiated in a predefined period of two weeks before and after 6 April, the date the new anticoagulation protocol was introduced. Data were collected for the complete consecutive period of renal replacement therapy for each patient. Filter circuits were individually allocated to the control group or high-dose anticoagulation group, based on the anticoagulation

Table 1. Overview of the anticoagulation methods of the control group and high-dose anticoagulation group, supporting CRRT in COVID-19 patients

	Control group	High-dose group
Heparin priming	None	5000 IU/l
Regional citrate pre-filter	2.2-3 mmol/l	3-3.5 mmol/l
LMWH	1dd 2850 IU	2dd 5700 IU

LMWH = low-molecular-weight heparin

used during the filter lifespan. Inclusion criteria were age over 18, active COVID-19 infection confirmed by PCR and renal failure requiring CRRT. Patients were excluded when CRRT was stopped within 72 hours for any reason or in case of indications for systemic anticoagulation at a therapeutic dosage other than COVID-19.

Anticoagulation

All patients were treated on a Baxter Prismaflex machine by use of the continuous venovenous haemofiltration (CVVH) modality and Baxter ST150 filters. Blood flow was set at 180 ml/min and ultra-filtrate rate at 2320 ml/h or 2620 ml/h for a patient weight of more than 90 kg with substitution flow at 1000 and 1300 ml/h, respectively. As post-dilution replacement solution Phoxillium, containing calcium, magnesium, sodium chloride, potassium, phosphate and bicarbonate, was used for all patients. The standard anticoagulation regime for CRRT consisted of RCA using a starting dose of 2.2 mmol/l administered pre-filter, which could be raised to a maximum of 3.0 mmol/l in case of recurrent circuit failure. This was supplemented by routine thrombosis prophylaxis with a single dose of LMWH, nadroparin, 2850 IU. In the control group, no unfractionated heparin was added to the priming solution.

The COVID-19 high-dose anticoagulation regime consisted of an increased RCA starting dose of 3.0 mmol/l, up to a maximum of 3.5 mmol/l. Routine thrombosis prophylaxis was increased to nadroparin 5700 IU twice daily.[14] A flowchart was introduced that allowed intensive care personnel to manage high filter pressure levels. In case of high filter pressure gradients, the blood flow was reduced to 150 ml/min. In the event of trans-membrane pressures exceeding 200 mmHg, the post-dilution replacement fluid rate was decreased by 50%, while blood flow was increased in order to meet the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guideline criterion of 25 ml/kg/h. See *table 1* for on overview of the anticoagulation methods.

Outcome

As primary outcome, the filter lifespan time was compared between the control and high-dose group. Additionally, the filter lifespan was compared with a historical group of non-COVID patients on CRRT in 2018. As secondary outcome, the systemic effects on serum ionised calcium, bicarbonate, pCO_2 and pH were evaluated based on arterial blood gas analysis. The final outcome was the occurrence of bleeding complications based on reported observations of blood loss by the nursing staff or reports of an unexplained fall of serum haemoglobin in the medical records.

Table 2. Main results on CRRT filter lifespan and systemic effects of anticoagulation in COVID-19 patients comparing the anticoagulation methods as described in table 1

	Control group	High-dose group	P value
Hours of CRRT	985.5	1627.5	NA
Filter sets	42	37	NA
Median filter lifespan, hours (IQR)	18 (20.3)	48 (44.5)	<0.001*
Serum calcium, mmol/l (IQR)	1.14 (0.10)	1.10 (0.09)	0,14
pCO_2, kPa (IQR)	7.28 (2.33)	6.70 (3.26)	0.02
Bicarbonate, mmol/l (SD)	26.1 (3.1)	28.4 (3.7)	<0.001*
pH (SD)	7.30 (0.09)	7.36 (0.10)	0.03

CRRT = continuous renal replacement therapy;
*indicates statistical significance

Statistical analysis

Data were analysed using SPSS statistics v23. The Shapiro-Wilk test was applied to test for a normal distribution. Continuous data were described as mean and standard deviation (SD) while the median and interquartile range (IQR) were provided if the distribution was skewed. As subgroup analysis, filter lifespan was compared in the patients receiving low-dose and subsequently high-dose anticoagulation in the course of their renal replacement therapy. Data on filter lifespan and blood gas analysis were considered as repeated measures and therefore dependent. To account for the asymmetry in number of observations per patient on low- and high-dose anticoagulation, a linear mixed model was set up to test significance of the effect of anticoagulation. The model was built step by step with the aim of minimising the model fitting error (-2LL) with the lowest number of degrees of freedom required. Anticoagulation was used as fixed effect as dichotomous variable in addition to a patient level random effect. Covariance structure was set at compound symmetry. More complexity was added to the model by changing the covariance structure to AR1, which presumes higher correlation between adjacent measurements, and adding a random intercept. These extra degrees of freedom did not lead to improved performance of the model and were therefore omitted in the final model. Significance threshold was set to 0.01 for all statistical tests in order to correct for multiple comparisons according to the Bonferroni correction method.[15]

Results

Nineteen patients requiring CRRT were eligible for inclusion, six patients were excluded since CRRT was stopped <72 hours and two because of an indication for therapeutic anticoagulation. Eleven ICU patients were included in the analysis. The mean age of these patients was 68 years and mortality was 45%; see *table 2* for the main results. The total duration of CRRT therapy amounted to 2613 hours, the individual length of CRRT ranging from 4 to 29 days. Two patients received low-dose anticoagulation, four patients high-dose anticoagulation while five patients received both regimes over the course of their renal replacement therapy. In total 79 filter sets were used, 42 filter sets were allocated to the control group and 37 filter sets to the high-dose group.

The results on filter lifespan, pCO_2 and calcium levels showed a non-normal distribution. The median filter lifespan was 18 hours (IQR 20.3) for the control group compared with 48.0 hours (IQR 44.5) in the high-dose group (p<0.001) *(figure 1)*. Bicarbonate levels were higher in the high-dose anticoagulation group, 28.4 compared with 26.1 mmol/l (p<0.001), while the median pCO_2 levels were comparable, resulting in a mean pH of 7.36 in the high-dose group compared with 7.30 (control), which was not significant (p=0.03). The serum ionised calcium levels were slightly lower in the high-dose group: 1.14 compared with 1.10 mmol/l (p=0.14). When considering only the five patients who received both low- and high-dose anticoagulation, totalling 55 filter runs, median filter lifespan was 12.5 hours (IQR 22) in the control group and 48 hours (IQR 42.5) in the high-dose group (p=0.001). Two bleeding events were observed in the high-dose group and none in the control group; one patient with a known bladder malignancy developed haematuria while on high-dose anticoagulation and in another patient oral blood loss was noted.

Discussion

The main finding of this report is that a combination of increased regional citrate and LMWH dose resulted in a significant increase of median filter lifespan time in ICU COVID-19 patients on CRRT.

The CRRT filter life in the group with routine RCA and thrombosis prophylaxis dose was considerably lower (mean 23.4 hours) than our historical mean filter lifespan in ICU patients at our institution in 2018: 33.6 hours. Recent studies on anticoagulation strategies report similar filter lifetimes for standard dose RCA for CRRT in COVID-19 patients.[12,16] These observations support that COVID-19 patients are prone to CRRT circuit thrombosis. In the high-dose group of our study, the resulting median filter lifespan of 48 hours exceeds previous results on anticoagulation by RCA combined with systemic heparin or therapeutic LMWH.[12,16] This could be related to a difference in case-mix since our baseline filter survival was higher. Alternatively, this could be related to the higher RCA dose used in our study.

The main disadvantages of increased RCA are risk of citrate accumulation and the need for more complex protocols.[17] RCA results in metabolic acidosis when clearance is diminished, or metabolic alkalosis when citrate clearance is optimal.[18] Consistently elevated bicarbonate levels were observed in the high-dose group. Because of concurrent elevated pCO_2 levels, this led on average to normalisation of the extracellular acid-base balance and to mild alkalosis on occasions. Additionally, citrate accumulation can lead to low ionised calcium. The observed level of serum ionised calcium was marginally lower in the high-dose anticoagulation group and did not reach statistical significance. Moreover, the median ionised calcium was above the lower target level that is generally considered safe and had a small range (IQR 0.09 mmol/l).[17]

Therapeutic dose,[19] but also intermediate dose LMHW,[20] have previously been reported to lead to more bleeding in critically ill COVID patients.[21] In our ICU-CRRT data we observed haemorrhage in two cases in the high-dose group and no bleeding events in the control group. While the small number of patients did not allow to confirm the causality of this observation, this finding warrants caution and a larger series will be needed to evaluate safety of high-dose anticoagulation. Based on an incidence of two bleeding complications in 37 CRRT filter lifetimes, a power of 0.80 and an alpha error of 0.05, a sample size of 300 filter runs would be required.[22]

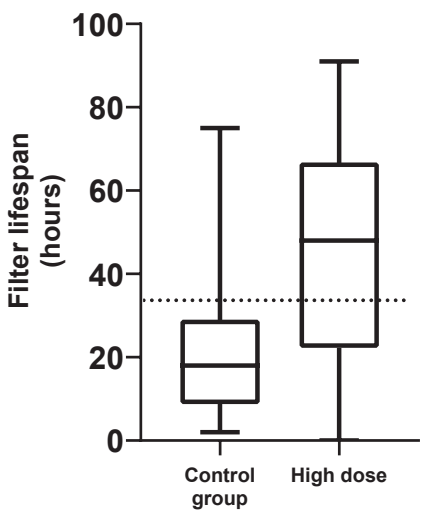

Figure 1. Boxplot of the CRRT filter lifespan showing the control group on the left and high-dose group on the right. The box represents the IQR (p25 - p75) with the line marking the median lifespan. The dashed line indicates the historic mean at our institution of CRRT filter lifespan of non-COVID-19 patients in the year 2018.

The main limitations of this study were the small number of patients and the non-blinded and non-randomised design. It is conceivable that differences in baseline characteristics, for instance platelet count[23] or use of vasopressors,[24] can act as confounders. While the small number of patients did not allow for adjustment of possible confounders, a subset analysis of five patients receiving both anticoagulation regimes showed similar outcomes. No conclusions can be drawn on the contribution of the individual anticoagulant measures on extending the filter lifespan but our results confirm previous findings reported by others.[11,12] A follow-up study, comparing the individual components in different groups would be required to quantify their effect. However, by sharing these early experiences, we aim to support the effective application of CRRT in ICUs during the COVID-19 pandemic.

Conclusion

Renal replacement therapy in COVID-19 patients is frequently complicated by thrombotic failure of the CRRT circuit resulting in reduced filter lifespan. The combination of increased regional citrate and LMWH dose appears to prolong filter lifespan in patients with COVID-19 while preserving systemic acid-base balance.

Disclosures

One of the authors worked at the St Antonius Hospital on a temporary basis because of the COVID-19 pandemic, her main employer is Baxter International Inc. No funding was received, and there was no potential financial gain for any of the involved parties. The other authors declare that they have no potential conflict of interest.

References

1. Baduashvili A, Oberle LP, Devitt J. Frequency of Continuous Renal Replacement Therapy Use Early in Coronavirus Disease 2019 Pandemic. Crit Care Explor. 2020;2:e0129.
2. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323:2052-9.
3. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost. 2020. Epub 2020/04/18.
4. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844-7.
5. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46:1089-98.
6. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost. 2020;18:1747-51.
7. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis Shutdown Correlation with Thromboembolic Events in Severe COVID-19 Infection. J Am Coll Surg. 2020;231:193-203 e1.
8. Yuan Q, Gao Z, Zhu D. Applying slope constrained Qbfs aspheres for asphericity redistribution in the design of infrared transmission spheres. Appl Optics. 2015;54:6857-64.
9. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-7.
10. Klok FA, Kruip M, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res. 2020;191:148-50.
11. Volbeda M, Londema M, van Meurs M, Stegeman CA, Gansevoort RT, Berger SP, van der Voort PHJ, Franssen CFM. A Method to Improve Continuous Renal Replacement Therapy Circuit Survival Time in Critically Ill Coronavirus Disease 2019 Patients With Acute Kidney Injury. Crit Care Explor. 2020;2(10):e0258.
12. Endres P, Rosovsky R, Zhao S, et al. Filter clotting with continuous renal replacement therapy in COVID-19. J Thromb Thrombolysis. 2021;51:966-70.
13. Bai M, Zhou M, He L, et al. Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs. Intensive Care Med. 2015;41:2098-110.
14. Vlot EA, Van den Dool EJ, Hackeng CM, Sohne M, Noordzij PG, Van Dongen EPA. Anti Xa activity after high dose LMWH thrombosis prophylaxis in covid 19 patients at the intensive care unit. Thromb Res. 2020;196:1-3.
15. Jafari M, Ansari-Pour N. Why, When and How to Adjust Your P Values? Cell J. 2019;20:604-7.
16. Volbeda M, Londema M, van Meurs M, et al. A Method to Improve Continuous Renal Replacement Therapy Circuit Survival Time in Critically Ill Coronavirus Disease 2019 Patients With Acute Kidney Injury. Crit Care Explor. 2020;2:e0258.
17. Davenport A, Tolwani A. Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. NDT plus. 2009;2:439-47.
18. Kramer L, Bauer E, Joukhadar C, et al. Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. Crit Care Med. 2003;31:2450-5.
19. Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. New Engl J Med. 2021;385:777-89.
20. Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA. 2021;325:1620-30.
21. Ten Cate H. Surviving Covid-19 with Heparin? New Engl J Med. 2021;385:845-6.
22. Wang H, Chow S-C. Sample Size Calculation for Comparing Proportions. Wiley Encyclopedia of Clinical Trials 2007.
23. de Pont AC, Bouman CS, Bakhtiari K, et al. Predilution versus postdilution during continuous venovenous hemofiltration: a comparison of circuit thrombogenesis. ASAIO J. 2006;52:416-22.
24. Dorffler-Melly J, de Jonge E, Pont AC, et al. Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors. Lancet. 2002;359:849-50.

Additionals

https://njcc.nl/sites/nvic.nl/files/21-17%20Lau%20STROBE_checklist_cohort.pdf