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Thrombosis Research 196 (2020) 1–3

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

# Anti Xa activity after high dose LMWH thrombosis prophylaxis in covid 19 patients at the intensive care unit

ARTICLE INFO

*Keywords:*
Covid-19
Viscoelastic coagulation tests
Thrombosis prophylaxis management
Anti Xa activity

ABSTRACT

*Introduction:* Coagulopathy in Coronavirus disease 2019 (covid-19) has been demonstrated by an increase in D-dimer, prothrombin time (PT), fibrinogen and factor VIII. Venous thromboembolic events are a common abnormality in patients with covid-19. We evaluate the results of intensive care unit (ICU) thrombosis prophylaxis of 5700 international unit (IU) nadroparin low molecular weight heparin (LMWH) twice daily.

*Methods:* After introduction of this high-dose pharmacological thrombosis prophylaxis twice weekly anti-factor Xa (anti Xa) concentrations and results from routine laboratory and viscoelastic hemostatic tests in 16 ICU covid-19 patients were evaluated.

*Results:* During one week, median peak anti Xa activities were 0.38 [0.16–0.45] and 0.38 [0.20–0.58] at time point 1 and 2 respectively. Laboratory coagulation tests showed PT, AT and platelet count (PltC) values within normal range and markedly increased D-dimer and fibrinogen levels. Viscoelastic tests showed a maximum clot strength just above normal reference value, while fibrin clot strength was strongly increased. The overall contribution of fibrin to clot strength was high with 71 [56–85]%.

*Conclusion:* Anti Xa activity was within the target range of pharmacodynamic endpoint for covid-19 patients but viscoelastic tests still demonstrated a procoagulant pattern.

Coronavirus disease 2019 (covid-19) is spreading rapidly around the globe after it was first recognized in Wuhan, China, in December 2019. The severe acute respiratory syndrome of coronavirus 2 (SARS-CoV-2) with its close proximity to the pulmonary capillary bed might allow systemic spread of virus to distant organs, especially in the context of inflammation and alveolar capillary leak [1].

Coagulopathy in covid-19 has been demonstrated by an increase in D-dimer, prothrombin time (PT), fibrinogen and factor VIII with a reported decrease in fibrinogen in non-survivors at days 10–14 [2,3].

While the pathophysiology underlying severe covid-19 remains incompletely understood, abnormal coagulation parameters were predominantly pro-thrombotic derangements of the haemostatic system that were associated with a poor prognosis [4,5]. This emphasizes the importance of screening for venous thromboembolism (VTE) at a low threshold because this appears to be a common abnormality in critically ill patients with covid-19. In a recent publication from 3 Dutch hospitals, the cumulative incidence of the composite outcome of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism was 31% (95%CI 20–41) [6]. This VTE rate could be underestimated since no systematic VTE screening was performed.

In view of this remarkably high VTE incidence in covid-19 patients we empirically increased our ICU thrombosis prophylaxis to high dose with 5700 IU nadroparin low molecular weight heparin twice daily; (LMWH BID and 7600 IU BID if body weight $>$ 120 kg) which is four times higher compared to regular ICU thrombosis prophylaxis (2850 IU once daily), hypothesizing that it may confer benefit to prevent microvascular thrombosis, but in the absence of randomized evidence [6]. The aim of the high-dose thrombosis prophylaxis was to remain below the therapeutic range of 0.6–1.0 IU/ml anti Xa peak concentration. Two weeks after introduction of this high-dose thrombosis prophylaxis twice weekly anti Xa concentrations were evaluated. In recent years the use of viscoelastic hemostatic assays has been the focus of research in management of coagulopathy after cardiovascular surgery, other major surgery and trauma [7]. To investigate if viscoelastic testing might have a role in understanding the coagulopathy in the group of covid-19 patients, thromboelastography (TEG) assay was performed.

Here we report anti Xa levels in ICU patients diagnosed with covid-19 upon this high-dose pharmacological thrombosis prophylaxis. In addition, results from routine laboratory and viscoelastic hemostatic tests are reported.

Data were obtained over a follow-up period of one week and comprised in total 16 ICU patients on mechanical ventilation. Five patients were admitted directly from the emergency department, two patients were transferred from other ICUs in the country, and the remaining 9 patients were admitted from the covid hospital wards. Data regarding medical history, medication use before hospital admission and laboratory data were collected from electronic patient files. Local Medical Research Ethics Committee approval was obtained with a waiver for patient informed consent due to the observational nature of the study.

For coagulation testing whole blood was sampled in 3.2% sodium citrate tubes (BD Vacutainer), performed at the hospital clinical chemistry laboratory. Daily performed coagulation analyses included PT, activated partial thromboplastine time (aPTT), D-dimer, fibrinogen, antithrombin activity (AT) and PltC. Blood sampling for anti Xa activity was performed twice a week with a measurement taken around 4 h after dosing (peak anti-Xa). PT, aPTT, D-dimer, AT and PltC were measured on a STA-Rack Evolution Coagulation system (Diagnostica Stago, Asnières, France) using respectively NeoPTimal (STAGO), PTT (a) STAGO, Tinaquant (ROCHE on a Cobas 7000 analytical system, liquid Fib (STAGO) for the Clauss methode, Liquid AT (STAGO). Plasma levels of anti-Xa activity were measured with a STA-Rack Evolution

https://doi.org/10.1016/j.thromres.2020.07.035
Received 2 May 2020; Received in revised form 15 July 2020; Accepted 17 July 2020
Available online 22 July 2020
0049-3848/ 

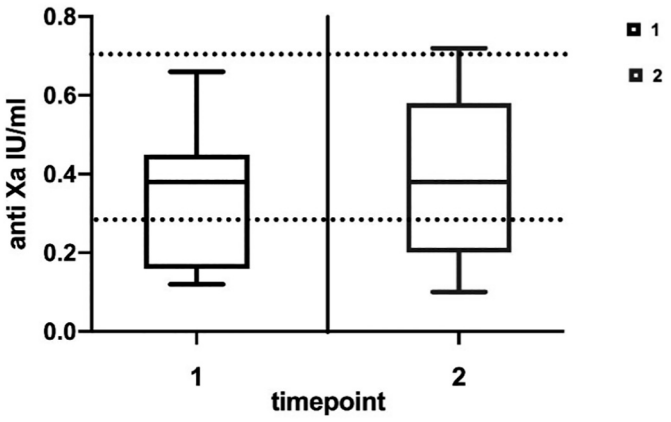


**Fig. 1.** Anti Xa activity.
Two timepoint data are presented as boxplot. Dashed lines indicate ISTH anti Xa activity reference range.

(Diagnostica Stago, Asnières, France) using an anti-Xa assay (STA®-Rotachrom® Heparin 4, Diagnostica Stago, Asnières, France). Global hemostasis viscoelastic tests were performed twice a week with TEG6S (Haemonetics Inc., Braintree, MA, USA) [8]. TEG6S system provides 4 assays in one multi channel cartridge. We assessed clot kinetics with K time (K; min) and clot strength with maximum amplitude (MA; millimeter; mm) on the standard citrated kaolin (CK) assay and fibrinogen clot strength with maximum amplitude (MA-CFF; min) on the citrated kaolin assay with GPIIb/IIIa inhibitor to block the platelet binding and aggregation. MA-CFF provides the overall contribution of fibrin to clot strength. Percentage contribution of fibrin to clot strength was calculated as MA-CFF divided by overall CK MA, the contribution of platelet function could be extrapolated.

Categorical data are stated as number or percentages. Continuous data are described as median, interquartile range [IQR] and range as all continuous variables were non-normally distributed. For statistical analysis IBM SPSS software version 24.0 for Windows was used (IBM Corp., Armonk, NY, USA). A $p$ value $< 0.05$ was considered statistically significant.

Median ICU length of stay at start of follow up was 20 [7–25] days. Median age was 67 [56–73] years, 12 (75%) was male, median body weight was 92 [83–99]kg and 9 (56%) had a history of hypertension. During follow-up no patients died, 2 patients were transferred to the ward after respiratory recovery and one patient was admitted to the ICU as a result of which 3 anti Xa samples (9%) were absent. In this observational study 5 anti Xa samples (16%) were missing. Six patients received continuous renal replacement therapy (CRRT) over the time course of ICU. CRRT patients received ICU covid-19 thrombosis prophylaxis. Since the start of high dose thrombosis prophylaxis management, no new PE was diagnosed and no systematic VTE screening was performed. Bleeding complications were limited to one patient with persistent blood loss from rectal hemorrhoids during use of a rectal stool cannula.

Median peak anti Xa activities were 0.38 [0.16–0.45] and 0.38 [0.20–0.58] at timepoint 1 and 2 respectively (Fig. 1). Peak anti Xa activity was not associated with bodyweight.

Table 1 reports median values of coagulation parameters. Laboratory coagulation tests showed PT, AT and PltC values within normal range and markedly increased D-dimer and fibrinogen levels. Viscoelastic tests showed a short but within normal range median clot kinetics time between split point and 20 mm amplitude clot strength due to fibrin cross linking. Maximum clot strength was just above normal reference value, while fibrin clot strength was strongly increased. The overall contribution of fibrin to clot strength was high with 71 [56–85]%.

The main finding of this report is that high-dose LMWH thrombosis prophylaxis in ICU covid-19 patients results in anti Xa peak level above the recommended antithrombotic prophylaxis anti Xa level of 0.1–0.3 IU/ml in regular medical and surgical ICU patients and within the International Society on Thrombosis and Hemostasis (ISTH) webinar recommended range of 0.3–0.7 IU/ml for covid-19 patients while anti Xa levels remained below therapeutic range of 0.6–1.0 IU/ml [9,10].

With increasing knowledge about a spectrum of coagulopathy in covid-19, the question that remains to be answered is when covid-19 patients should be treated with high-dose thrombosis prophylaxis or therapeutic anticoagulation and which dosing regimen is preferred. The presented data contribute to the understanding of anti Xa concentrations with the chosen high-dose thrombosis prophylaxis of 5700 IU LMWH twice daily and could be helpful in the search for optimal prophylaxis and treatment of VTE in ICU covid-19 patients. For the management of dosing, monitoring of anti Xa activity may be useful especially when patients are at risk of LMWH accumulation and increased bleeding risk with low body weight or diminished renal function.

Despite anti Xa activity within the covid-19 target range of pharmacodynamic endpoint, viscoelastic tests still demonstrated a procoagulant pattern. In normal individuals platelets are known to contribute more than half of total clot strength but in covid-19 patients clot strength is dominated by the fibrin component.

It is unknown whether high dose thrombosis prophylaxis may prevent VTE or improve outcome in covid-19 ICU patients and it is unclear how to guide its management. The optimal dosing in patients with severe covid-19 remains unknown and warrants further prospective randomized investigation. At this moment it is unclear whether viscoelastic testing may have additional value in monitoring coagulopathy or the effect of the high-dose pharmacological thrombosis prophylaxis in covid-19 patients. Further studies are needed to assess the usefulness and limitations of this technology in these critically ill patients with a hypercoagulable state. Besides early testing it would be interesting to measure the contribution of platelet function and thrombin generation

**Table 1**
Coagulation parameters.

| Timepoints | | 1 | Missing | 2 | Missing |
|---|---|---|---|---|---|
| | Normal range | $N = 16$ | | N = 16 | |
| PC (*$10^9$/l) | | 347 [302–462] (264–556) | 1 | 341 [304–437] (237–775) | 2 |
| D-dimer (ug/l) | < 500 | 4425 [1870–5781] (307–7089) | 2 | 3147 [2226–5466] (463- > 8000) | 2 |
| PT (s) | 12.0–15.5 | 14.5 [14.0–15.4] (13.0–16.3) | 1 | 14.6 [13.9–15.2] (13.3–16.5) | 2 |
| APTT (s) | 30.0–36.5 | 42.1 [36.6–48.9] (33.9–56.3) | 1 | 37.9 [33.7–42.3] (29.3–47.9) | 2 |
| Fibrinogen (g/l) | 2.0–4.0 | 6.2 [5.9–6.9] (5.1–8.9) | 1 | 6.6 [5.2–7.3] (4.5–7.9) | 2 |
| AT (%) | 80–120 | 81 [76–92] (53–118) | 1 | 81 [74–88] (62–109) | 2 |
| CK-K (s) | 0.8–2.1 | 0.8 [0.8–1.0] (0.6–1.3) | 4 | 0.8 [0.7–1.0] (0.6–1.3) | 3 |
| CK-MA (mm) | 52–69 | 71 [69–74] (68–80) | 4 | 70 [68–72] (66–78) | 3 |
| CFF-MA (mm) | 15–32 | 51 [45–57] (40–62) | 4 | 48 [39–58] (36–62) | 3 |

Data are presented as median [IQR] (range).

to clot strength in covid-19 patients. The main limitation of this pilot is the single arm. Additional limitations are the small sample size and missing values because of the introduction of a new routine diagnostic test and the observational nature of the study.

## Acknowledgements

None.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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E.A. Vlot[a,*], E.J. Van den Dool[b], C.M. Hackeng[b], M. Sohne[c], P.G. Noordzij[a], E.P.A. Van Dongen[a]
[a] *Department of Anesthesiology, Intensive Care and Pain medicine, St Antonius Hospital, the Netherlands*
[b] *Department of Clinical Chemistry, St Antonius Hospital, the Netherlands*
[c] *Department of Hematology, St Antonius Hospital, the Netherlands*
*E-mail address:* e.vlot@antoniusziekenhuis.nl (E.A. Vlot).

[*] Corresponding author at: Department of Anaesthesia, Intensive Care and Pain Medicine, St Antonius Hospital, Koekoekslaan 1, 3430 EM Nieuwegein, the Netherlands.