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Targeted interventions in mechanically ventilated patients

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PART II

ANTI- COAGULANT TREATMENT

ABSTRACT

Introduction

Pulmonary embolism (PE) is a frequent complication in Coronavirus disease 2019 (COVID-19) patients. The pathogenesis of COVID-associated activation of coagulation is not fully understood, which makes it uncertain whether unfractionated heparin (UFH), or anticoagulation in general, is effective. The aim of this study is to determine the effects of intravenous UFH on clinical, radiological and laboratory parameters in patients with COVID-19 and PE.

Materials and Methods

We conducted an observational cohort study in 19 Intensive Care Unit (ICU) patients with COVID-19 and computed tomography (CT) scanning proven PE. According to the local protocol, repeated CT-scanning was indicated if no pulmonary improvement was present after 7 days following start of anticoagulant treatment. We defined three endpoints: laboratory markers (d-dimer at day 0 vs day 2), clinical success (resolution of PE at follow-up CT-scan or discharged alive from ICU) and radiological response (Qanadli index at follow-up CT-scan vs CT scan at diagnosis PE). Statistical tests used were a T-test and Wilcoxon Signed Rank test.

Results

UFH resulted in clinical success in 14 out of 19 patients. Pulmonary emboli were completely resolved on the follow-up CT-scans in 5 out of 6 patients and partly resolved in the 6th patient. D-dimer levels decreased on average from 7074 ng/mL to 4347 ng/mL ($p=0.001$) within 48 hours after start of UFH.

Conclusion

In this observational study, we showed a rapid clinical, laboratory and radiological improvement in patients with COVID-19 and proven PE. Standard anticoagulant treatment was effective in this setting, supporting current guideline recommendations.

BACKGROUND

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a firm grip on public health globally since December 2019. To this date, over 35 million people have been infected worldwide with more than 1 million deaths (1). Patients with progressive disease almost invariably show profound pulmonary inflammation and may require mechanical ventilation and prolonged Intensive Care Unit (ICU) admission. Mortality rates in ICU patients can reach up to 50% (2). Despite adequate thromboprophylaxis the majority of patients are in a prothrombotic state which results in thrombotic complications, mainly pulmonary embolism, in up to 31% of the cases (3-6).

The pathogenesis of Corona Virus Disease 2019 (COVID-19)-associated activation of coagulation is currently not fully understood. It differs from disseminated intravascular coagulation (DIC) as seen in patients with sepsis. In DIC coagulopathy is initiated by tissue factor leading to consumption of platelets and coagulation factors with thrombocytopenia and prolonged PT and APTT (7). In contrast, in patients with COVID-19, d-dimer levels are high (up to 20.000 ng/mL or higher), but platelets and coagulation tests are normal in most patients suggesting a different mechanism of activation of coagulation and a high rate of fibrin degradation (8). Differences between COVID-19 pulmonary embolism (PE) and non – COVID-19 PE have been also been observed in Computed Tomography (CT) findings, suggesting that COVID-19 associated PE has a different phenotype than 'conventional' PE. In COVID-19 patients PE is frequently located in peripheral lung segments and less extensive compared to PE in patients without COVID-19. It has been hypothesized that the coagulopathy in COVID-19 patients may be driven by a local process associated with severe pulmonary inflammation and in situ thrombosis (9).

Established PE is treated with anticoagulants, which often is unfractionated heparin (UFH) in patients in cardiocirculatory shock or respiratory distress (10). As the pathophysiology of coagulation in COVID-patients is unknown, it is uncertain whether UFH -or anticoagulation in general- is effective in the attenuation of the procoagulant state. Since insufficient treatment of PE can be fatal, this observational study aims to study the effect of UFH on clinical, radiological and laboratory signs of PE in patient with COVID-19.

MATERIAL AND METHODS

Patient selection

This observational cohort study was conducted in the ICU of the Leiden University Medical Center (LUMC) in the Netherlands. This study was approved by the Institutional

Review Board of the LUMC for COVID-19 studies. The need for consent was waived by the Institutional Review Board of the LUMC for COVID-19 studies. Inclusion criteria were age >18 years, proven COVID-19 disease by PCR sampling of nasal/oral airway swab, mechanical ventilation, proven PE documented by CT scanning and treatment with unfractionated heparin. Exclusion criteria were: therapeutic doses of UFH within 48 hours prior to the diagnosis of PE, treatment with reperfusion techniques including fibrinolytic drugs or no data on d-dimer levels prior to the start of UFH therapy. Standard treatment included prophylactic low molecular weight heparin (LMWH) with nadroparin 2850 IU/day subcutaneously or 5700 IE/day if bodyweight >90 kg. Double prophylactic LMWH was defined as nadroparin 5700 IE/day. According to the local protocol, repeated CT-scanning was indicated if no pulmonary improvement was present after a minimum of 7 days following start of anticoagulant treatment.

Clinical and biological data

Data was collected for a maximum of 21 days or until ICU discharge. The following clinical and laboratory data were extracted from medical records: age, sex, year of birth, body mass index (BMI), date of ICU admission, date of ICU discharge, reason for discharge, condition 28 days after admission, starting time of UFH therapy and available D-dimer levels which were measured as a part of routine care every day. D-dimer has been measured in citrated plasma on a STA-R MAX analyzer with latex-based immunoturbidimetric reagents from STAGO BNL, Leiden, the Netherlands. Successful treatment was defined as either no PE on follow-up CT or survival at ICU discharge.

CT data acquisition and analysis

A CT-scan was performed in case of suspected PE. Standard contrast-enhanced CT pulmonary angiography (CTPA) was performed using a 320-MDCT scanner (AquilionONE, Canon) with collimation of 80 x 0.5 mm section thickness. Rotation time was 0.275 second, with a helical pitch of 65. Tube current was with automated exposure control and tube voltage was 100 kVp. The amount of iodinated contrast (Xenetix 350) was 50-80 mL with a flow of 4.5-6.0 mL/s followed by a saline flush of 45-50 mL. Images were reconstructed with 1 and 3 mm thickness using AIDR 3D enhanced technique. All scans were evaluated on a dedicated PACS workstation by a radiologist with >20 years of experience in chest CT. The diagnosis of PE was established on CTPA based on filling defect in a pulmonary artery. The thrombus load within the pulmonary arteries was determined by using the Qanadli obstruction index and calculated as percentage vascular obstruction (11). Parenchymal lung tissue involvement regarding pathology due to COVID-19 infection and pre-existing pathology, comprising a composition of ground-glass- or alveolar consolidation, atelectasis, emphysema, and fibrosis, was visually assessed by evaluation of axial, coronal, and sagittal reconstructions and expressed as percentage.

Outcomes

We defined three endpoints: Laboratory markers (d-dimer at day 0 vs day 2), clinical success (resolution of PE at follow up CT scan or discharged alive from ICU) and radiological response (Qanadli index at follow up CT scan vs CT scan at diagnosis PE). Severe bleeding was defined according to the definition of the International Society on Thrombosis and Haemostasis (ISTH) of 'major bleeding in non-surgical patients' (12).

Statistical analysis

Statistical analysis was performed by using IBM SPSS statistics version 25. Normality of the data was tested using the Shapiro-Wilk-test. Normally distributed data are presented as means with standard deviation (SD); data outside normal distribution are presented as medians with interquartile range (IQR). Categorical variables are presented as numbers and percentages. To calculate a significant difference between the two groups, a T-test and Wilcoxon Signed Rank test was used. A two-sided $p < 0.05$ was considered statistically significant. The graphs are created using GraphPad Prism version 8.

RESULTS

In total, between March 15 and May 1st 2020, 90 patients were admitted to the ICU with confirmed COVID-19. Nineteen patients fulfilled the in- and exclusion criteria (Figure 1).

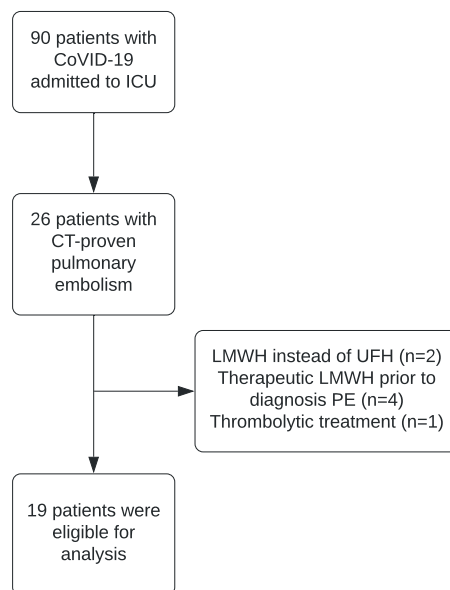


Figure 1. Flow chart of patient selection

All patients were mechanically ventilated and had PE proven by CT-scanning. Baseline, radiological and laboratory characteristics are shown in Table 1 and 2. All patients received either prophylactic, or double prophylactic doses of thromboprophylaxis with nadroparin (low molecular weight heparin (LMWH)) which was switched to therapeutic unfractionated heparin when the diagnosis of PE was confirmed.

Table 1. Baseline characteristics

<i>Patient characteristics</i>	
Mean Age, year (SD)	63 (6.6)
Male, n(%)	16 (84)
Mean body mass index, kg/m ² (SD)	27.5 (2.8)
Thrombosis prophylaxis when admitted at ICU	
- Prophylactic, n (%)	16 (84.2)
- Double prophylactic, n (%)	2 (10.5)
- Therapeutic, n (%)	0 (0)
- Unknown, n (%)	1 (5.3)
Status at 28 days after admission	
- ICU, n (%)	9 (47.4)
- Hospital, n (%)	5 (26.3)
- Death, n (%)	2 (10.5)
- Rehabilitation, n (%)	1 (5.3)
- Home, n (%)	1 (5.3)
- Other, n (%)	1 (5.3)

Table 2. Radiological and laboratory characteristics

<i>Radiological presentation</i>	
Qanadli index first CT, mean (%) $\pm$ SD	17.5 ($\pm$ 10.8)
Location pulmonary embolism on first index CT	
- Subsegmental, n(%)	2 (10.5)
- Segmental, n(%)	16 (84.2)
- Main/lobar, n(%)	1 (5.3)
Patients with follow-up CT	6
Qanadli index first follow-up CT	
- 0% (n)	5
- 5% (n)	1
<i>D-dimers</i>	
D-dimers day -2 Median + IQR	5379 ng/mL (2460-10604)
D-dimers day -1 Median + IQR	5555 ng/mL (4317-9769)
D-dimers day 0 Median + IQR	6197 ng/mL (4682-9360)
D-Dimers day 1 Median + IQR	4766 ng/mL (3047-7773)
D-dimers day 2 Median + IQR	3665 ng/mL (2470-5437)

Radiological outcome

The mean Qanadli index of the CT-scans before start of heparin was 17.5% (SD 10.8%), with the segmental artery being the most frequent location of the thrombi. Follow-up CT-scans were performed in 6 patients with an average follow-up of 18 days. The Qanadli index decreased significantly from baseline to follow-up ($p=0.03$ for difference with baseline CT-scan). A Qanadli index decrease to 0% was observed in 5 patients and a decrease to 5% was seen in the remaining patient. Two patients had a third follow-up CT-scan. In one patient there was already no remainder of PE on the first follow-up CT-scan and in the other patient the CT-scan remained stable with a Qanadli index of 5% at 25 days. Both were still receiving heparin at the time of the second follow-up CT-scan.

Clinical outcome

In at least 14 (74%) patients, UFH treatment was successful: in 6 patients (32%) PE was found to be completely resolved on follow-up CT, whereas 8 patients (42%) were discharged from the ICU following clinical improvement. One patient died in the ICU without follow-up CT-scan to evaluate treatment. From the remaining 4 (21%) patients it is unknown whether treatment was successful, because they were transferred to another ICU.

At 28 days after admission 9 (47.4%) patients were still in the ICU (including 3 of the 4 patients that were eventually transferred to another ICU), 7 (36.8%) patients were discharged from the ICU to either the nursing ward ($n=5$, 26.3%), a rehabilitation center ($n=1$, 5.3%) or home ($n=1$, 5.3%). In total, 2 (10.5%) patients died (of which 1 had clinical improvement on the follow-up CT) in the ICU and 1 (5.3%) was transferred to another ICU.

In our cohort, 6 patients (32%) suffered from bleeding complications, of which 2 patients (10.5%) were classified as severe bleeding. These severe bleedings were located in the lung ($n=1$) and the lower gastrointestinal tract ($n=1$). None of these bleedings resulted in death.

Laboratory outcome

D-dimer levels from all patients from approximately 2 days before the start of heparin until 21 days after start heparin or until ICU-discharge are shown in Figure 2. The percentage change of D-dimer levels in relation to start of heparin per 24-hours period from two days before UFH to 2 days after start of UFH are shown in Figure 3. All blood samples used to determine D-dimer levels were taken at 6 AM. Therefore $T=0$ in this graph represents the D-dimer taken at 6 AM at the day UFH was started. The actual start of UFH varied for every patient. Mean start of heparin was 9 hours (SD 4.9) after blood sampling. From the first time point, from day -2 to day -1, the D-dimer dropped

on average 6.7% (SD 26.9) after which, from day -1 to day 0, it increased 5.6% (SD 25.6). The first day after start of UFH, a mean drop of 17.9% (SD 19.4) and the second day a drop of 14.6% (SD 15.9) was seen. The average D-dimer at day 0 was 7074ng/mL compared to 4347ng/mL at day 2 ($p=0.001$). The mean difference from day 0 to day 2 was -2810ng/mL (95%CI -721 ng/mL to -4347 ng/mL).

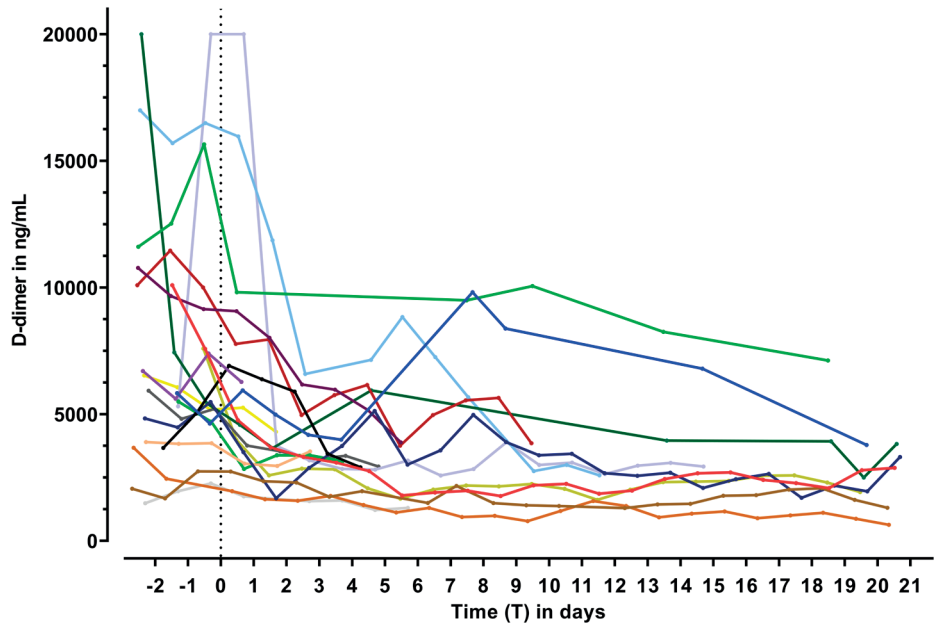


Figure 2. Course of D-dimers before and after start of heparin. D-dimer levels from 2 days before the start of UFH until 21 days after start of UFH or until ICU discharge are shown. T=0 represents the start of heparin for each individual patient, which is marked by the dotted line.

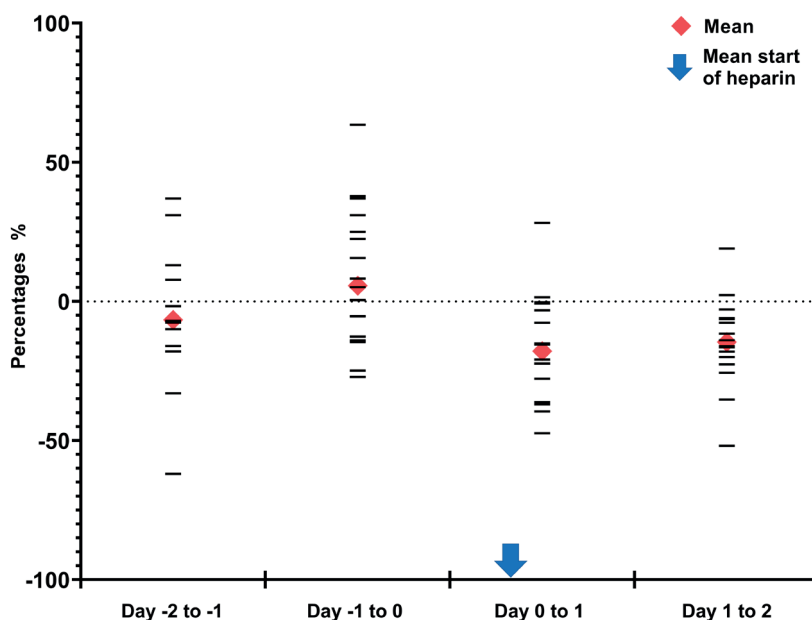


Figure 3. Percentage change of D-dimer levels for different time frames before and after start of heparin. All samples were taken at 6:00 A.M. For every patient T=0 represents the time of blood sampling at 6:00 AM of the day that heparin was started. The horizontal lines represent the percentage change in that time frame for each individual patient. The arrow represents the mean actual time of start of heparin.

DISCUSSION

In this study we show that clinical and radiological signs of PE and plasma D-dimer levels decreased after administration of UFH in patients with COVID-19 and PE. This is the first study on the effect of heparin (either UFH or LMWH) on thrombosis in COVID-19 patients. Earlier, Tang and others (13) studied the effect of LMWH in 449 COVID-19 patients. They found an association between increasing D-dimer and higher mortality in non-LMWH treated patients. Also, a reduced mortality was seen in patients with coagulopathy who were treated with LMWH compared with patients with coagulopathy who were not treated with LMWH (40% vs 64.2%, $p=0.029$). However, the effect of UFH on D-dimer levels or PE resolution was not reported.

Despite the fact that our results suggest that therapeutic UFH is an effective treatment of COVID-19 associated PE, thrombo-embolic complications are common despite prophylactic LMWH (3, 14). An explanation for this might be the route of administration or the dose. Giving subcutaneous LMWH prophylaxis in the ICU might lead to lower

anti-Xa activity by the concurrent use of vasoconstrictors such as norepinephrine (15). Norepinephrine was also administered in most COVID-19 patients in the ICU (data not shown). Furthermore, prophylactic doses of LMWH are lower than therapeutic doses and result in lower anti-Xa activity. Consequently, anticoagulant effects will be lower and may be insufficient to prevent PE. It is currently unknown if increasing the doses of LMWH would be beneficial in preventing thrombotic complications in COVID-19 patients. Some authors suggest to treat severe COVID-19 pneumonia, even without serious obstructive signs of pulmonary embolism, with thrombolysis in order to improve oxygenation (16). However, our results show that those measures are not necessary: regular treatment is effective and can resolve PE on short notice. Therefore we support current guideline recommendations to reserve thrombolysis to patients with high-risk PE and apply standard dose thromboprophylaxis.

There have been concerns about a high incidence of Chronic Thrombotic Pulmonary Hypertension (CTEPH) after COVID-19 associated PE, in particular because inflammatory states have been associated with poor thrombus resolution.(17, 18). Although our sample size is small, the rapid clot resolution observed in our study suggests that the incidence of CTEPH in COVID-19 associated PE survivors may not be notably increased. Even so, physicians should remain vigilant on the presence of CTEPH in patients treated for COVID-19 associated PE who have not been recovered after a 3-month follow-up period.

In our study population with UFH, 6 out of 19 patients experienced bleeding complications with 2 severe bleeding episodes. To properly outweigh the risk of bleeding and the risk of thrombosis, properly designed randomized controlled trials (RCTs) are needed to establish the optimal dose and route of administration for COVID-19 patients. Currently, several RCTs are underway (19).

Our study had several limitations. The change in D-dimer levels may have been influenced by other factors than administration of UFH. A fall in D-dimer may for instance also reflect an improvement of the inflammatory state. In this uncontrolled observational study we cannot exclude confounding by factors modifying the severity of illness. Therefore, the decline in D-dimers that we found in the two days after start of heparin could also be caused by clinical improvement in general. Another limitation is the limited sample size of 19 patients with only 6 patients having had a follow-up CT scan. Strongpoints of the study include the strict protocol in our ICU dictating repeated CT-scanning if no improvement of pulmonary status was present after one week of treatment of UFH, and the meticulous comparison of index and follow-up CTPA scan images.

CONCLUSION

In conclusion, we show a considerable clinical and radiological improvement in patients with COVID-19 and proven PE after starting UFH therapy. Standard anticoagulant treatment therefore seems to be effective in this setting, supporting current guideline recommendations.

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