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Diagnosis, management, and outcomes of venous thromboembolism in COVID-19 positive patients: a role for direct anticoagulants?

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Abstract
Coronavirus disease 2019 (COVID-19) has been associated with an increased risk of thromboembolic complications due to systemic coagulation activation. Little is known about the role of direct anticoagulants (DOACs) in COVID-19 related thrombosis. In this audit we sought to distinguish COVID-19 hospitalised patients with a diagnosis of venous thromboembolism (VTE) and record their outcomes over a period of 3 months (01/02/2020–30/04/2020). A total of 1583 patients were diagnosed with laboratory proven COVID-19 disease. Amongst them, 38 patients (0.82%) suffered VTE (median age 68 years, male/female: 20/18). VTE was the presenting symptom on admission in 71%. Pulmonary embolism was diagnosed in 92% of patients; 5 patients required intensive care and 3 underwent thrombolysis. 27 patients received initial treatment with unfractionated heparin/low molecular weight heparin (LMWH) while 10 were treated with direct anticoagulants (DOACs). After a median follow up of 25 days, 29 (76%) patients were alive while 5 were still hospitalised. Most patients (83%) were discharged on DOACs, no VTE recurrence or bleeding was recorded post-discharge. Our results suggest that direct anticoagulants could be a safe and effective treatment option in selected COVID-19 positive patients who have suffered venous thromboembolism.

Keywords COVID-19 · Direct anticoagulants · Venous thromboembolism · Heparin · D-dimers

Highlights

- COVID-19 has been associated with an increased risk of thromboembolic complications, mainly in the intensive care setting.
- 38 consecutive patients with COVID-19 and venous thromboembolism (VTE) and their subsequent management, are described. Most patients (33/38) were treated on general wards.
- Treatment with direct oral anticoagulants (DOACs) upon VTE diagnosis, appears effective in selected COVID-19 patients.
- Most patients (83%) were discharged on DOACs without any complications.
- DOACs could be considered in the design of prospective clinical trials focusing on COVID-19 related VTE.

Introduction

Coronavirus disease 2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the biggest pandemic in the last 100 years. It has resulted so far in more than five million confirmed cases and about 347,000 fatalities. COVID-19 may predispose patients to both arterial and venous thrombotic events, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis [1]. Publications of small cohorts of patients suggest that thromboembolism is principally a complication of severe

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COVID-19 requiring intensive care support [2–5]. In this setting, the wider consensus is to use heparin preparations for anticoagulation treatment [1]; Very little has been published about the role of direct anticoagulants (DOACs), although it has been suggested that the current health crisis offers numerous arguments for favouring anticoagulation with DOACs in patients without contra-indications [6].

In this study, we sought to characterize VTE in a wider COVID-19 patient population in our institution, and to rationalize the subsequent anticoagulation strategies in this setting.

Methods

Patient population

We undertook an audit to identify COVID-19 hospitalised patients with a diagnosis of venous thromboembolism (VTE) and record their outcomes over a 3-month period (01/02/2020–30/04/2020). We investigated all adult patients with laboratory-proven COVID-19 admitted to Birmingham Heartlands, Good Hope and Solihull hospitals.

Objectives

We aimed to describe the characteristics of VTE in hospitalised COVID-19 patients and record their outcomes.

Data collection

Patient anonymised data were retrospectively reviewed for demographics, clinical and laboratory findings, treatment, and outcomes at time of VTE. Data collection ended on 08/05/2020. Subsequently, data was independently verified by two physicians and a clinical pharmacist in terms of VTE diagnosis and treatment.

Outcomes

The primary outcome was a clinical diagnosis of venous thromboembolism. The secondary outcomes were VTE recurrence following initiation of therapeutic anticoagulation and major bleeding as per the ISTH criteria [7].

Statistics

Study population characteristics were reported by using standard descriptive statistics.

Results

Between 01/02/2020 and 30/04/2020, a total of 1583 symptomatic patients were diagnosed with COVID-19 as confirmed by RNA detection of the SARS-CoV-2 at the Public Health England Birmingham laboratory. Amongst them, 38 patients (0.82%) were admitted to hospital and developed VTE during their stay. Their demographics and significant medical history are displayed in Table 1. Their laboratory picture at the time of VTE diagnosis is shown in Table 2.

Most patients (71%) were diagnosed with VTE on admission, at the time where they were also tested for SARS-CoV-2. Eleven patients (29%) developed VTE after being found SARS-CoV-2 positive. Five out of 11 (55%) patients were on prophylactic low molecular weight heparin

Table 1 Patient characteristics (N = 38)

Male	20 (53%)
Female	18 (47%)
Median age (range)	68 years (29 to 91)
Timing of acute VTE event	
VTE present at time of COVID-19 disease diagnosis	27 (71%)
VTE occurring post COVID-19 disease diagnosis	11 (29%)
Median time from COVID-19 positivity (range)	11 (6–33) days
On thromboprophylaxis at time of VTE event	5 (55%)
COVID-19 related significant medical history	24 (73%)
Cardiac history	6
Atrial fibrillation	3
Ischaemic heart disease	2
Infective endocarditis	1
Asthma/COPD	6
Active cancer	6
Metastatic solid tumour	4
Localised solid tumour	1
Non-Hodgkin's lymphoma	1
On immunosuppressive medication	5
Rheumatoid arthritis	2
Lupus	1
Neurosarcoidosis	1
Nephrotic syndrome	1
Diabetes on treatment	5
Reduced mobility due to recent fall	3
Vascular dementia	2
Morbid obesity	1
Pregnancy	1
Previous VTE	1

VTE venous thromboembolism, *COPD* chronic obstructive pulmonary disease

Table 2 Laboratory picture at time of VTE diagnosis

Median WBC count, $\times 10^9$/L (range)	9.4 (2.69–31.6)
Median Neutrophil count, $\times 10^9$/L (range)	5.65 (1.56–26.53)
Median Lymphocyte count, $\times 10^9$/L (range)	0.62(0.33–3.31)
Lymphopenia, < 0.7	13/38 patients (34%)
Median Platelet count, $\times 10^9$/L (range)	292 (107–717)
Thrombocytopenia, $< 150 \times 10^9$/L	8/38 patients (21%)
Median D-Dimer count, ng/mL (range)	2945(462–59,554)
Median Fibrinogen levels, g/L (range)	5.05(0.6–7.5)
Hypofibrinogenaemia, < 1.5	1/38 patients (3%)
Median INR, (range)	1.1 (0.9–2.7)
Abnormal INR, > 1.2	7/33 patients (21%)
Median aPTT ratio, (range)	1.0 (0.7–1.6)
Abnormal aPTT, > 1.2	2/33 patients (6%)
Median CRP, mg/L (range)	98.5 (2–474)
Median Ferritin, µg/L (range)	713 (12–8392)

VTE venous thromboembolism, *WBC* white blood cells, *INR* international normalised ratio; aPTT, activated partial thromboplastin time, *CRP* C reactive protein

(LMWH) when VTE occurred. At the time of thrombosis, 4 were inpatients and were on regular LMWH thromboprophylaxis while 7 (18%) were outpatients, recently discharged with a diagnosis of mild COVID-19. While five of the seven outpatients had risk factors for VTE (reduced mobility: two, metastatic cancer: one, on tamoxifen: one, pregnancy: one, recent infective endocarditis: one), only one of them was on prophylactic LMWH. Median time from SARS-CoV-2 positivity to VTE diagnosis was 11 (6–33) days (Table 1).

Venous thromboembolism diagnosis and immediate therapy

Thirty-four patients were diagnosed with pulmonary embolism (PE). Amongst them seven patients were deemed too unstable to have CT pulmonary angiography. Although radiological confirmation of PE was not obtained, they were treated as such based on clinical, laboratory, ECG and echocardiogram findings. One pregnant patient suffered a combined PE and stroke 6 days post-delivery. Only three patients were diagnosed with deep vein thrombosis (DVT), two out of three DVTs were related to central venous catheter insertion.

Thirty-three patients received general ward-based care while five patients were escalated to intensive care. Three patients required thrombolysis. Twenty-seven patients were treated with unfractionated heparin (3/27) or LMWH (24/27) for their VTE. Ten patients were initiated on DOACs, none of them was on lopinavir, ritonavir, or darunavir at the time. One patient was not offered anticoagulation due to active bleeding not related to COVID-19 (Table 3).

Table 3 Patient clinical outcomes (N = 38)

Main thrombotic event	
Pulmonary embolism	34 (89%)
Confirmed clinical and radiological diagnosis	27 (70%)
Presumed clinical diagnosis	7 (19%)
Combined pulmonary embolism and stroke	1 (3%)
Deep vein thrombosis	3 (8%)
Catheter related	2
Proximal DVT	1
Hospital site	
Ward	33 (87%)
Intensive care unit	5 (13%)
Immediate VTE treatment	
Thrombolysis	3 (8%)
Unfractionated heparin/ LMWH	27 (71%)
Direct anticoagulants	10 (26%)
Apixaban	8
Rivaroxaban	2
No anticoagulation	1 (3%)
Treatment outcomes (recorded on 08/05/2020)	
Median follow up time (range)	25 (2–86) days
Alive patients	29 (76%)
Discharged	24
Still inpatients	5
Dead patients	9 (24%)
Median time to death (range)	4 (0–22) days
VTE recurrence	1 (3%)
Bleeding while on anticoagulation	0 (0%)
VTE therapy upon discharge (N = 24)	
LMWH	3 (13%)
Direct anticoagulants	20 (83%)
Apixaban	16
Rivaroxaban	3
Edoxaban	1
No anticoagulation/temporary IVC filter insertion	1 (4%)

DVT deep venous thrombosis, *LMWH* low molecular weight heparin, *VTE* venous thromboembolism, *IVC* inferior vena cava

Outcomes

At the time of data analysis (08/05/2020), 5 patients were still in hospital, 9 had died from COVID and 24 had been discharged. Most patients were sent home on DOACs (83%). Only 3 patients continued therapeutic LMWH while one patient was kept off anticoagulation (see above) and had a temporary inferior vena cava filter inserted (Table 3).

Median follow up time on 08/05/2020 was 25 (2–86) days. Only one inpatient with a history of lupus and antiphospholipid antibody positivity experienced recurrence of his DVT in a different anatomical location, while on LMWH treatment. Following discharge, no VTE recurrence has been recorded so far.

No major bleeding events related to COVID-associated coagulopathy or therapeutic anticoagulation were identified in our study. Most of our patients had a normal coagulation profile and platelet count (Table 2).

Discussion

Our paper describes our experience with patients who were mainly treated for COVID-19 and VTE at general wards; only 5/38 patients required intensive care. So far, most evidence in the field has come from published papers focused on VTE management in the intensive care setting [2–5, 8].

We reported a VTE incidence of 0.82% in symptomatic SARS-CoV-2 positive patients. This may represent an underestimate. It is possible but unknown that VTE remains underdiagnosed in patients with severe COVID-19 who are deemed eligible for palliative care only. Recent papers from Netherlands and Italy reported a VTE occurrence of 3% and 6.6% respectively in non-ICU COVID-19 patients admitted to general wards [4, 5]. Undoubtedly VTE frequency is much higher in COVID-19 patients requiring critical care, ranging from 25 to 47% [5, 8].

Thirty five out of 38 (92%) of our VTE patients were diagnosed with PE while Isolated DVT was identified in only 3/38 (8%). This paucity of DVT diagnosis in our paper is probably related to two facts; In our institution patients on palliative care were not investigated for VTE. Also, screening for lower extremity DVT was only offered to COVID patients with a high clinical suspicion of DVT. Isolated DVTs have been found to account for 31–42% of total VTE events in other studies [4, 5].

In our study 71% of patients had VTE at the time of SARS-CoV-2 testing while 21% returned to hospital with a VTE after being discharged with a diagnosis of mild COVID-19. Our results indicate that thromboembolic complications may represent an integral part of the clinical picture of COVID-19 and be already present at the time of initial diagnosis and at the time of disease progression.

Our paper raises the question about whether ambulatory patients with mild COVID-19 should be offered thromboprophylaxis. Although almost every inpatient is risk assessed for VTE and prescribed pharmacological and/or mechanical thromboprophylaxis, routine thromboprophylaxis is not widely accepted in ambulatory patients with acute medical illness or respiratory symptoms [9, 10]. In the absence of evidence coming from prospective randomised trials, an individualized stratification of VTE risk for COVID patients upon discharge would be advisable. Extended prophylaxis might be considered when immobilization is prolonged during a lengthy illness or recovery phase or when other VTE risk factors like pregnancy or active cancer are present.

Offering effective thromboprophylaxis in COVID-19 patients remains a challenge. A high failure rate of conventional LMWH dosage has been described, predominantly in the intensive care setting. At present, while medical practitioners use a variety of prophylactic, intermediate, or therapeutic doses of anticoagulants in patients, the optimal dosing for patients with severe COVID-19 remains unknown and warrants further investigation [1]. Currently, 12 prospective clinical trials studying different LMWH doses, are in the process of recruiting or are about to open (www.cinicaltrials.gov, accessed on 14/05/2020).

Unfractionated heparin (UFH) and LMWH appear to be the treatment of choice in COVID-19 related VTE. In severely ill inpatients with thromboembolism, UFH is preferred as it may be temporarily withheld and has no known drug-drug interactions with investigational COVID-19 therapies. Concerns with UFH, however, include the time to achieve therapeutic anticoagulant levels and the increased healthcare worker exposure for frequent blood draws to monitor the blood thinning effect [1]. Therefore, LMWH may be preferred in patients unlikely to need procedures. Anticoagulant therapy with LMWH appears to be associated with better prognosis n severe COVID-19 patients with coagulopathy [11]. The anti-inflammatory function of heparin, its ability to 'protect' the endothelium and lessen the microcirculatory dysfunction may also be relevant in this setting [12].

What could the role of DOACs in COVID-19 related venous thromboembolism be? DOACs appear to have equal antithrombotic efficacy compared to vitamin K antagonists (VKAs) or heparins, proven safety, and ease of use in many therapeutic or preventive indications [6]. Comparable to heparin, thrombin or factor Xa inhibition could also be associated with an anti-inflammatory effect [13]. The benefits of oral anticoagulation with DOACs include the rapid onset and offset of action, lack of need for monitoring, facilitation of discharge planning, and outpatient management.

What are the likely risks of using DOACs in COVID patients? DOACs have a longer half-life compared to UFH and LMWH which is a disadvantage when invasive procedures are required urgently or when COVID inpatients deteriorate clinically or develop renal impairment [14]. Another risk may include a potential bioavailability-related effect on clinical effectiveness through interactions with drugs currently used in COVID like antivirals, antibiotics, and steroids. DOAC bioavailability depends on P-glycoprotein (P-gp) and CYP3A4-type cytochrome P450 metabolism. Antivirals like ritonavir and lopinavir and macrolides like clarithromycin and erythromycin can increase DOAC levels through CYP3A4 inhibition. Dexamethasone can decrease DOAC levels through strong P-gp and CYP3A4 induction [1]. During the current COVID-19 pandemic, concerns have been raised about the safety of

concomitant use of DOACs and antivirals like lopinavir, ritonavir and darunavir; an Italian study has identified a significant increase of DOAC plasma levels in SARS-CoV-2 positive patients who were treated with antivirals. Although the authors did not report any bleeding outcomes, they suggested withholding DOACs from patients with severe SARS-CoV-2 infection and replacing them with parenteral anticoagulation for as long as antiviral agents are deemed necessary [15]. DOAC level measurement appears to have a limited role in everyday clinical decision making [16]. Furthermore, the formal guidance in the setting of antiviral therapy with lopinavir and ritonavir advises against the use of rivaroxaban and edoxaban while apixaban can be given at 50% of the recommended dose; dabigatran does not require any dose adjustment [1]. There are no known interactions between DOACs and remdesivir or ribavirin (www.asahq.org, accessed on 21/05/2020).

No bleeding events were recorded in our patient cohort. Although this might look exceptional, it is probably related to the fact that most of our patients had normal coagulation parameters (Table 2). Compared to the high incidence of thrombotic events, bleeding complications are considerably rare in COVID-19 patients [1]

We report here our experience of VTE diagnosis and management in COVID-19 patients. As a single institution and retrospective study, there are a number of limitations to this work; We describe a relatively small cohort of patients. Our patient group had a comparatively short median follow-up time of 25 (2–86) days, which offers only partial insight into the risk of VTE recurrence. Additionally, there was no prior assignment of patients to different treatment options, and the observational design makes comparisons between patients inappropriate. However, our report results from the systematic analysis of real life VTE patients with COVID-19. Its strength is that it describes an alternative and effective strategy to deal with such patients. In our study, selected haemodynamically stable VTE patients were treated with DOACs from the first day of their diagnosis. Upon discharge, most of our patients were also given DOACs. We did not identify any VTE recurrence and no bleeding events were recorded. Based on our findings we believe that DOACs could be considered in the design of prospective clinical trials focusing on COVID-19 related VTE.

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Compliance with ethical standards

Conflict of interest C. Kartsios reports research support and lecturing or consultancy fees, outside the present work, from Bayer, Daiichi Sankyo, Bristol Meyers Squibb, and Pfizer. The other authors have no disclosures.

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