Characterization of the Benefits and Risks of Therapeutic Anticoagulation in Patients Admitted with Severe COVID-19 (CRITAC)

Alison Jinn, Michael Kammermayer, Vincent H Mabasa, Tracy Liu, Tarnvir Sonia Paul, and Nam Phan

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ABSTRACT

Background: Severe COVID-19 is associated with increased rates of thrombotic complications. Recent provincial recommendations in British Columbia have suggested providing thromboprophylaxis with therapeutic anticoagulation for hospital inpatients with severe COVID-19 who do not have a high risk of bleeding.

Objectives: To characterize the rates of major bleeding, thrombotic events, complications from COVID-19, and adverse effects among patients with severe COVID-19 treated with therapeutic anticoagulation.

Methods: This retrospective chart review involved patients with laboratory-confirmed COVID-19 who were admitted to 3 sites within a local health authority between April 1 and December 31, 2021, and received therapeutic anticoagulation for thromboprophylaxis.

Results: After screening of 1036 patients, 72 patients were included in the study. The mean age of participants was 54 years, 63% (n = 45) were male, and 92% (n = 66) were receiving supplemental oxygen by nasal prongs on admission. The primary outcome, major bleeding, was experienced by 1 patient (1%). Increasing oxygen requirements resulting in progression to high-flow nasal cannula occurred in 11 patients (15%), and 5 patients (7%) required admission to the intensive care unit. One patient (1%) experienced a thrombotic event, and 1 patient (1%) had a minor bleed. The mean duration of hospitalization was 10 (standard deviation 10.8) days. One death occurred during the study period, and no cases of heparin-induced thrombocytopenia were observed.

Conclusions: In this study of hospital inpatients with severe COVID-19 who were deemed to be at low risk of bleeding and who received therapeutic anticoagulation, there were low rates of both major bleeding and thrombotic events.

Keywords: COVID-19, therapeutic anticoagulation, thromboprophylaxis, low-molecular-weight heparin

RÉSUMÉ

Contexte : Les cas graves de COVID-19 sont associés à des taux accrus de complications thrombotiques. De récentes recommandations provinciales en Colombie-Britannique proposent de fournir une thromboprophylaxie avec anticoagulation thérapeutique aux patients hospitalisés atteints d'une forme grave de COVID-19 qui ne présentent pas un risque élevé de saignement.

Objectifs : Caractériser les taux d'hémorragies majeures, d'événements thrombotiques, de complications découlant de la COVID-19 et d'effets indésirables chez les patients atteints de COVID-19 sévère traités par anticoagulation thérapeutique.

Méthodes : Cette revue rétrospective des dossiers portait sur des patients atteints de COVID-19 confirmée en laboratoire qui ont été admis dans 3 sites au sein d'une autorité sanitaire locale entre le 1er avril et le 31 décembre 2021 et qui ont reçu une anticoagulation thérapeutique pour la thromboprophylaxie.

Résultats : Après la présélection de 1036 patients, 72 ont été inclus dans l'étude. L'âge moyen des participants était de 54 ans, 63 % (n = 45) étaient des hommes et 92 % (n = 66) recevaient un supplément d'oxygène par sonde nasale à l'admission. Le critère de jugement principal, une hémorragie majeure, a été observé chez 1 patient (1 %). Une augmentation des besoins en oxygène entraînant une progression vers une canule nasale à haut débit s'est produite chez 11 patients (15 %) et 5 patients (7 %) ont dû être admis à l'unité de soins intensifs. Un patient (1 %) a présenté un événement thrombotique et 1 patient (1 %) a eu un saignement mineur. La durée moyenne d'hospitalisation était de 10 jours (écart type 10,8). Un décès est survenu au cours de la période d'étude et aucun cas de thrombocytopénie induite par l'héparine n'a été observé.

Conclusions : Dans cette étude portant sur des patients hospitalisés atteints d'une forme grave de COVID-19, considérés comme présentant un faible risque de saignement et ayant reçu une anticoagulation thérapeutique, les taux d'hémorragies majeures et d'événements thrombotiques étaient faibles.

Mots-clés : COVID-19, anticoagulation thérapeutique, thromboprophylaxie, héparine de bas poids moléculaire

INTRODUCTION

COVID-19 has led to a global pandemic and is associated with high rates of morbidity and mortality.[1] Typically, severe SARS-CoV-2 infections are characterized by respiratory compromise, but current evidence also shows increased rates of thromboembolic complications such as venous thromboembolism.[2,3] The rate of thromboembolic events is at least 3 times higher among patients hospitalized with COVID-19 than among those admitted with other viral respiratory infections.[4] Although the exact pathophysiology is not completely understood, it has been proposed that COVID-19 may directly damage both pneumocytes and vascular endothelial cells, resulting in increased platelet aggregation, coagulability, and inflammation. Further disease progression can then result in thrombosis and microthrombosis.[2,5]

Since the discovery of hypercoagulability with COVID-19, several trials have been conducted to assess the benefit of therapeutic anticoagulation for patients hospitalized with COVID-19.[6-10] Dosing regimens that have been reported in the literature include therapeutic anticoagulation with enoxaparin at 1 mg/kg subcutaneously twice daily as well as thromboprophylactic dosing with enoxaparin at 40 mg subcutaneously twice daily.[6,9] A recent multiplatform randomized controlled trial (RCT) showed that treating non–critically ill COVID-19 patients with therapeutic anticoagulation resulted in increased probability of survival to hospital discharge, with reduced use of intensive care unit (ICU)–level organ support relative to thromboprophylactic dosing.[6] Analysis of secondary outcomes in this RCT showed insufficient evidence for a reduction in mortality and a minor increase in major bleeds in the group that received therapeutic anticoagulation.[6] The results of this RCT have led to changes in therapeutic recommendations, such as those of the British Columbia COVID-19 Therapeutics Committee (BC CTC), which now suggest therapeutic anticoagulation with low-molecular-weight heparin (LMWH), unless contraindicated, for non–critically ill young people and adults with COVID-19.[11,12] In addition, since the initiation of the trial reported here, the HEP-COVID and RAPID RCTs have also found reductions in thrombotic events or death with therapeutic anticoagulation for hospitalized COVID-19 patients.[13,14] However, several retrospective cohort studies have shown no differences in rates of mortality or invasive mechanical ventilation with the use of therapeutic anticoagulation relative to thromboprophylactic dosing, with an increased risk of major bleeding in the therapeutic anticoagulation group.[8-10] Given the variability in evidence for the benefits of therapeutic anticoagulation and the potentially increased risk of bleeding in patients hospitalized with COVID-19, further studies are needed to determine the value of this practice as standard management for COVID-19 hypercoagulability.

In April 2021, the BC CTC suggested that patients hospitalized with severe COVID-19 and without a high risk of bleeding receive therapeutic anticoagulation with LMWH (preferred) or unfractionated heparin within 72 hours of admission, with treatment to be continued for 14 days or until discharge.[12] The purpose of our study was to characterize the rates of major bleeding, thrombotic events, complications from COVID-19, and adverse effects in patients with severe COVID-19 who were treated with therapeutic anticoagulation, to assess the effect of this practice change on patient outcomes.

METHODS

Study Design

A retrospective chart review was conducted to assess the safety of thromboprophylaxis with therapeutic anticoagulation in patients with confirmed COVID-19 admitted to 3 Fraser Health Authority sites in British Columbia between April 1 and December 31, 2021. Because of prespecified time limitations, this 9-month inclusion period was chosen to capture a sample size of convenience.

Population

The study population was determined by means of cross-referencing independent computer-generated reports from the patient records system. One report, from the Fraser Health Authority's pharmacy informatics department, was programmed to identify all adult patients (≥ 17 years old) admitted to a medical unit who received care according to the COVID-19 preprinted order sets. The other report, from the Fraser Health Authority's health records department, was programmed to identify all adult patients admitted to a medical unit with laboratory-confirmed COVID-19. Eligible patients were those with a confirmed diagnosis of COVID-19 (positive for SARS-CoV-2) and severe disease requiring supplemental oxygen therapy above baseline requirements who had been started on therapeutic anticoagulation with LMWH or unfractionated heparin within 72 hours after hospital admission and continued for at least 48 hours. We included patients with laboratory-confirmed COVID-19 based on a positive result on polymerase chain reaction testing at the time of admission to hospital or in the community before admission. Patients with a negative result on COVID-19 testing at the time of admission were included if they tested positive during their admission and were subsequently treated (within 72 hours of the positive result) with at least 48 hours of therapeutic anticoagulation with LMWH. Severe COVID-19 was defined as disease not requiring organ support, such as high-flow nasal cannula (HFNC), vasopressor/inotropes, extracorporeal membrane oxygenation, or invasive or noninvasive ventilation. Potential participants were excluded if they had a high risk of bleeding (age

≥ 75 years, estimated glomerular filtration rate < 30 mL/min, platelet count < 50 × 10^9/L, receipt of dual-antiplatelet therapy, serious gastrointestinal bleeding or intracranial condition within the past 3 months, epidural or spinal catheter), a high risk of bleeding into a critical site, active bleeding of clinical significance requiring intervention, known major bleeding disorder, or acquired coagulopathy; if they were already receiving therapeutic anticoagulation for another indication; or if they had known heparin allergy, including heparin-induced thrombocytopenia. The hospital's electronic records for eligible patients were reviewed to collect baseline data, as well as data for the primary and secondary outcomes with the use of a standardized data collection table, as agreed upon by the research team.

Sample Size

A convenience sample size of 100 participants was targeted, and participants were randomly screened for eligibility until this sample size was achieved. Only patients admitted on or after April 1, 2021, were included, as this date aligns with the implementation of the BC CTC recommendation to use therapeutic anticoagulation for thromboprophylaxis in patients with severe COVID-19 and low bleeding risk.

Outcomes

The primary outcome was the proportion of patients who experienced major bleeding, defined by the International Society on Thrombosis and Haemostasis as fatal bleeding and/or symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial bleeding or intramuscular bleeding with compartment syndrome) and/or bleeding causing a fall in hemoglobin level of 20 g/L or more or leading to transfusion of 2 or more units of whole blood or red cells.[15] Secondary outcomes were selected to determine the prevalence of potential complications from either COVID-19 or thrombotic events, as well as adverse effects from therapeutic anticoagulation, and are consistent with outcomes studied in RCTs with larger sample sizes.[6,13,14] The secondary outcomes were the rates of progression to requiring HFNC, progression to requiring admission to ICU, thrombotic events (venous thromboembolism, stroke, or acute coronary syndrome), minor bleeding, all-cause mortality, and heparin-induced thrombocytopenia, as well as the duration of hospitalization.

Statistical Analysis

The data were analyzed using descriptive statistics, and the results are reported using means and proportions.

As a quality improvement study, this research protocol was granted an exemption from ethics review by the Fraser Health Research Ethics Board.

RESULTS

A total of 1036 patients were screened, of whom 72 were included in the study (Figure 1). The main reasons for exclusion were absence of treatment with therapeutic anticoagulation and initiation of HFNC within 72 hours after admission. The mean age of participants was 54 years, 63% were male, 92% were receiving supplemental oxygen by nasal prongs at the time of admission, and 10% had chronic respiratory disease at baseline. For all patients included in the study, an LMWH was prescribed for therapeutic anticoagulation. The complete baseline characteristics of the included patients are reported in Table 1.

Primary Outcome

The primary outcome occurred in 1 patient (1%), who met the criterion of bleeding causing a fall in hemoglobin level of at least 20 g/L or leading to transfusion of at least 2 units of whole blood or red cells (Table 2). This outcome occurred

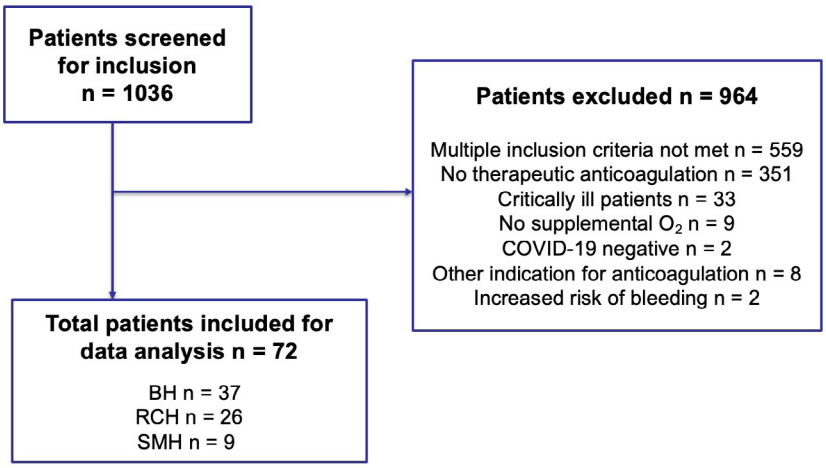

FIGURE 1. Patient flow chart. BH = Burnaby Hospital, RCH = Royal Columbian Hospital, SMH = Surrey Memorial Hospital.

in a 69-year-old patient with hypertension who required a nonrebreather mask for oxygen delivery on presentation. The patient received therapeutic anticoagulation with LMWH for 13 days and was then transferred to the ICU because of increasing oxygen requirements and initiation of HFNC. Therapeutic anticoagulation was discontinued upon transfer to the ICU. Thirteen days after discontinuation of therapeutic anticoagulation, the patient experienced a drop in hemoglobin of at least 20 g/L, leading to transfusion of more than 2 units of packed red blood cells; the patient was later found to have gastrointestinal bleeding from a gastric ulcer. The patient was stabilized following the transfusion and survived to hospital discharge.

TABLE 1. Demographic and Baseline Characteristics

Characteristic	No. (%) of Patients[a] (*n* = 72)
Age (years) (mean ± SD)	54 ± 14
Sex, male	45 (63)
Weight (kg) (mean ± SD)[b]	87.2 ± 19.3
No. with readmission	0
Pre-existing condition	
Hypertension	23 (32)
Diabetes mellitus	17 (24)
Chronic respiratory disease	7 (10)
Chronic kidney disease	7 (10)
Coronary artery disease	4 (6)
Immunosuppression	2 (3)
Liver disease	2 (3)
History of venous thromboembolism	1 (1)
History of cerebrovascular accident	0 (0)
Oxygen therapy on presentation	
Nasal prongs	66 (92)
Nonrebreather mask	5 (7)
Face mask	1 (1)
Medications that increase risk of bleeding	
Antiplatelet agents	3 (4)
Selective serotonin reuptake inhibitors	3 (4)
Nonsteroidal anti-inflammatory drugs	2 (3)
Anticoagulants	0 (0)
Therapeutic anticoagulation prescribed	
Low-molecular-weight heparin	72 (100)
Unfractionated heparin	0 (0)

SD = standard deviation.
[a]Except where indicated otherwise.
[b]Weight not available for 11 patients.

TABLE 2. Primary Outcome

Outcome	No. (%) of Patients (*n* = 72)
With major bleeding	1 (1)
Type of bleeding	
Fatal bleeding	0 (0)
Symptomatic bleeding in a critical area or organ	0 (0)
Bleeding causing a fall in hemoglobin ≥ 20 g/L, or leading to transfusion of ≥ 2 units of whole blood or red cells	1 (1)

Secondary Outcomes

The mean duration of hospitalization was 10 (standard deviation 10.8) days. Eleven patients (15%) had increasing oxygen requirements resulting in progression to HFNC, and 5 patients (7%) required admission to the ICU (Table 3). There was 1 thrombotic event, which occurred in a patient who had increasing oxygen requirements that resulted in progression to HFNC and admission to the ICU. A pulmonary embolism was diagnosed 7 days after the discontinuation of therapeutic anticoagulation. Another patient experienced a minor bleed, specifically, an episode of hemoptysis that led to therapeutic anticoagulation being held for 48 hours before the patient's discharge to home. There were no cases of heparin-induced thrombocytopenia during the study period, and there was 1 death secondary to worsening respiratory failure.

DISCUSSION

We found a low occurrence of both major bleeding and thrombotic events among patients hospitalized with severe

TABLE 3. Secondary Outcomes

Outcome	No. (%) of Patients[a] (*n* = 72)
Progression to requirement for HFNC	11 (15)
Progression to requirement for admission to ICU[b]	5 (7)
Thrombotic event	
Venous thromboembolism (deep vein thrombosis)	0 (0)
Venous thromboembolism (pulmonary embolism)	1 (1)
Stroke	0 (0)
Acute coronary syndrome	0 (0)
Minor bleeding	1 (1)
All-cause mortality	1 (1)
Heparin-induced thrombocytopenia	0 (0)
Duration of hospital stay (days) (mean ± SD)	10 ± 10.8

HFNC = high-flow nasal cannula, ICU = intensive care unit, SD = standard deviation.
[a]Except where indicated otherwise.
[b]Out of 68 patients (4 patients were not eligible for ICU admission according to their code status).

COVID-19 who, upon admission, had a low risk of bleeding and were subsequently treated with therapeutic anticoagulation. A previous multiplatform trial, which was to date the largest trial evaluating therapeutic anticoagulation in inpatients with COVID-19, reported a 1.9% rate of major bleeding.[6] Similarly, in the HEP-COVID and RAPID trials, the rates of major bleeding among inpatients with COVID-19 who were receiving therapeutic anticoagulation and were admitted to medical wards were 2.4% and 0.9%, respectively.[13,14] In the current study, just 1 (1%) of 72 patients experienced major bleeding during treatment with therapeutic anticoagulation, which aligns with the rates in these previous trials and may indicate that our patient population had a similar risk of bleeding with therapeutic anticoagulation. Furthermore, the single episode of major bleeding in our study occurred 13 days after discontinuation of therapeutic anticoagulation; as such, there is a low likelihood that this bleed was related to the course of therapeutic anticoagulation.

Because this trial did not have a comparison arm, the results were compared with existing data to assess whether our population and findings were similar to existing evidence. In terms of baseline characteristics, the average age in our study was 54 years and the comorbidities included hypertension (32%), diabetes (24%), and chronic respiratory disease (10%). In previous trials, the average age was about 60 years, with 48% to 63% of patients having hypertension, 30% to 40% having diabetes, and 7% to 22% having chronic respiratory disease.[6,13,14] As such, the patients in the current study may have been slightly younger with lower rates of comorbidities than those in previous studies; overall, however, the patients in all of these trials were generally healthy with few comorbidities.

In the RCTs with treatment arms that received therapeutic anticoagulation, the rates of thrombotic events among inpatients with COVID-19 were 0.9%[14] and 1.4%.[6] In our study, 1% (n = 1) of the patients who received therapeutic anticoagulation experienced a thrombotic event; this may signify that our study population had a risk of thrombotic events similar to that of the populations studied in previous trials. The episode of pulmonary embolism in our study occurred when the patient was in the ICU, 7 days after discontinuation of therapeutic anticoagulation; therefore, we are unable to assess whether this thrombotic event would have occurred if the patient had continued receiving therapeutic anticoagulation. The low event rates in our study suggest that our inclusion and exclusion criteria allowed for the selection of patients with COVID-19 who may have derived benefit from therapeutic anticoagulation and did indeed have a low risk of bleeding.

The mean duration of hospitalization in our study was 10 days, similar to the mean duration of 12.2 days in a previous trial.[13] There were no cases of heparin-induced thrombocytopenia, and the mortality rate was 1%, which are both in keeping with previous trials.[6,14] The rate of admission to the ICU was 7%, lower than the 14.5% rate reported in a previous trial.[14] This difference may be due to the slightly younger, healthier population in our study, and potentially to increased vaccination rates in our study population, given the time during which this trial was conducted.

Although, like the current study, the HEP-COVID study[13] limited inclusion of patients receiving therapeutic anticoagulation to those who were also receiving supplemental oxygen, the requirement for supplemental oxygen was not an inclusion criterion for the multiplatform trial.[6] Even so, 88% of patients in the multiplatform trial ultimately received supplemental oxygen.[6] Thus, for consistency with the previous trials, and because this is what was recommended by the BC CTC at the time, we limited our inclusion of patients treated with therapeutic anticoagulation to those who were also receiving supplemental oxygen. This allowed for the selection of patients who would have been at the lowest risk and who would have had the greatest potential benefit from this intervention.

Strengths and Limitations

To our knowledge, this is the first study within the Fraser Health Authority looking at the safety of the use of therapeutic anticoagulation for thromboprophylaxis in inpatients with severe COVID-19 considered to be at low risk of bleeding. Given the variability of results obtained in previous trials, the results of our trial may aid clinicians in assessing the appropriateness of this new intervention for patients in their local settings. This multisite study had event rates similar to those described in previous trials, which gives us confidence that these are likely comparable to rates for the patient population within the Fraser Health Authority. Therefore, our study results are anticipated to be applicable to other sites within our local health authority and can provide additional evidence and reassurance to clinicians throughout the Fraser Health Authority.

Our study had several limitations. We were unable to achieve the target sample size, which limited the number of patients assessed for outcomes and thus limits generalizability of the results to a larger patient population. Nonetheless, it is reassuring that our results are similar to those reported in previous trials.[6,13,14] Our inability to achieve the target sample size may have been due to changes in the wording of local recommendations during the study period. In November 2021, the BC CTC changed the wording from "therapeutic anticoagulation is suggested" to "therapeutic anticoagulation may be considered" in patients without high-risk features for serious bleeding and not requiring organ support. Although we were aware of this change, we could not extend the study timeframe because of timeline restrictions. In addition, although all 3 sites used the same preprinted order based on the BC CTC recommendations, there may have been varying degrees of uptake across the

sites in terms of prescribing therapeutic anticoagulation for severely ill patients with COVID-19. The reports of the pharmacy informatics and health records departments represented a comprehensive list of patients who had a diagnostic code for COVID-19 or who received care according to the COVID-19 preprinted order sets.

Very few events were observed in our study, which limits our ability to characterize patient-specific risks and benefits or to identify potential trends among the patients who experienced events. By following the recommendations from the BC CTC, we included a very specific population of COVID-19 patients with low risk of bleeding based on strict inclusion and exclusion criteria.[12] As is true for all trials involving patients with COVID-19, our study was limited to patients with the COVID-19 variants that were prevalent during the study period. Different variants may have different rates of disease severity and thrombotic events, and our data may therefore not reflect current or future event rates. Ongoing event-rate analyses, as well as studies with control groups, are needed to allow more comprehensive evaluation of the benefits and risks of therapeutic anticoagulation in this patient population.

CONCLUSION

Our study demonstrated low rates of major bleeding and thrombotic events, similar to those previously seen with the use of therapeutic anticoagulation in patients with severe COVID-19 and low bleeding risk.

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Alison Jinn, BSc(Pharm), ACPR, was, at the time of this study, a Postgraduate Year 1 Resident with Lower Mainland Pharmacy Services, Fraser Health Authority, Burnaby, British Columbia. She is now a Clinical Pharmacist with the Pharmacy Department, Royal Columbian Hospital, New Westminster, British Columbia.

Michael Kammermayer, BSc, PharmD, ACPR, was, at the time of this study, a Clinical Pharmacy Specialist – Internal Medicine with the Pharmacy Department, Burnaby Hospital, Burnaby, British Columbia, and is now the Clinical Pharmacy Supervisor with the same department and hospital.

Vincent H Mabasa, BSc(Pharm), ACPR, PharmD, is the Clinical Pharmacy Coordinator with the Pharmacy Department, Burnaby Hospital, Burnaby, British Columbia.

Tracy Liu, PharmD, ACPR, is a Clinical Pharmacist with the Pharmacy Department, Burnaby Hospital, Burnaby, British Columbia.

Tarnvir Sonia Paul, MD, is a Hospitalist with Burnaby Hospital, Burnaby, British Columbia.

Nam Phan, MD, is a Hospitalist with Burnaby Hospital, Burnaby, British Columbia.

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Address correspondence to:
Alison Jinn
Pharmacy Department
Royal Columbian Hospital
330 East Columbia Street
New Westminster BC V3L 3W7

email: Alison.jinn@fraserhealth.ca

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