

Anticoagulation Therapy Using Unfractionated Heparin at a Therapeutic Dose for Coronavirus Disease 2019 Patients With Severe Pneumonia: A Retrospective Historical Control Study

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Abstract

Introduction: Patients with severe coronavirus disease 2019 (COVID-19) pneumonia often have the complications of coagulopathy and thrombotic phenomena, which lead to high mortality. Whether administering systematic anticoagulant therapy is beneficial remains unclear. We report our experience using systemic anticoagulation with unfractionated heparin to treat severe COVID-19.

Methods: We conducted a retrospective historical control study of severe COVID-19 patients requiring mechanical ventilation who received prophylactic-dose anticoagulation (April 1–May 20) or therapeutic-dose anticoagulation (May 21–August 20) in the intensive care unit (ICU) of the tertiary emergency critical care medical center in Japan. The primary endpoints were in-hospital mortality and anticoagulation therapy-related adverse events. The secondary endpoints included the administration of veno-venous extracorporeal membrane oxygenation (ECMO), ventilator-free days (VFD), ICU-free days, and the development of multiple organ dysfunction syndrome.

Results: Twenty-one patients were in the prophylactic-dose group and 26 patients were in the therapeutic-dose group. Background characteristics between the groups were not significantly different, although the therapeutic-dose group had a lower in-hospital mortality rate [0 (0.0%) patients vs. 4 (19.0%) patients; $p = 0.063$] and significantly longer ICU-free days (median [interquartile range (IQR)]: 15 days [13-18] vs. 5 days [0-13]; $p = 0.014$). Hemorrhagic events did not occur during the study period. Compared to the prophylactic-dose group, the therapeutic-dose group tended to have a longer VFD, were not treated with ECMO, and did not experience multiple organ dysfunction syndrome; however, the difference was not statistically significant.

Conclusions: Therapeutic-dose anticoagulation may be beneficial for patients with severe COVID-19 pneumonia requiring mechanical ventilation.

Introduction

The novel coronavirus disease 2019 (COVID-19) is an emerging disease that has increased rapidly since first being identified in China in December 2019 [1, 2]. COVID-19 induces a cytokine storm that activates the coagulation cascade, thereby resulting in coagulopathy and thrombotic phenomena, which lead to multiple organ dysfunction and high mortality [3]. COVID-19-related deaths could be largely attributed to hypoxemia secondary to acute respiratory distress syndrome; however, a growing suspicion is that thromboembolic events could also affect clinical outcomes [4]. Patients with severe COVID-19 pneumonia often have coagulopathy that is similar to other systemic coagulation abnormalities associated with severe infections such as disseminated intravascular coagulation or thrombotic microangiopathy; however, the mechanism of COVID-19-related coagulopathy has different features [5].

A previous statement on the management of COVID-19 -related coagulopathy suggested the use of heparin at a prophylactic dose for all COVID-19 patients [6]. Expert recommendations for the use of anticoagulants for patients with high thrombotic risk exist [7–9]. Furthermore, a recent large cohort study

[10] reported that the use of anticoagulation at treatment doses may be associated with a reduced risk of mortality among hospitalized patients with COVID-19, regardless of the route of administration. However, no data have supported therapeutic-dose anticoagulation for all patients with severe COVID-19 pneumonia [11]. Based on this background, we hypothesized that the administration of therapeutic-dose anticoagulant therapy in the early phase of intensive care unit (ICU) admission would be beneficial for patients with severe COVID-19.

Methods

Study design and setting

This study was a single-center retrospective historical control study conducted at the ICU of the tertiary emergency critical care medical center (Tokyo, Japan). The medical records of COVID-19 patients with severe pneumonia who were admitted between April 1, 2020 and August 20, 2020 were reviewed. In the hospital, the therapeutic strategy for anticoagulation was changed on May 20, 2020, at which point the dose of heparin was altered from the prophylactic dose to a therapeutic dose. The clinical outcomes of patients who received prophylactic or therapeutic doses of heparin were compared. The study was approved by the institutional review board of our hospital (approval number: M2020-130). The board waived the need for written informed consent because this study was retrospective.

Patient population

Consecutive severe COVID-19 patients requiring mechanical ventilation who were admitted to the ICU of Tokyo Medical and Dental University Hospital of Medicine (Tokyo, Japan) were included. A diagnosis of COVID-19 was determined for all patients, based on findings of the nasopharyngeal swab test for SARS-CoV-2 by using real-time reverse transcriptase polymerase chain reaction. All included patients received prophylactic-dose anticoagulation or therapeutic-dose anticoagulation during their ICU stay. We excluded patients with 'do not attempt resuscitation' orders [including ventilation, veno-venous extracorporeal membrane oxygenation (ECMO), and renal replacement therapy (RRT)] and patients who had missing or insufficient data regarding study variables. Patients whose anticoagulation therapy strategy was changed (e.g., from prophylactic dose to a dose to maintain ECMO or RRT circuit) within the first 48 hours after administration of mechanical ventilation were also excluded because the aim of this study was to evaluate the effect of the early administration of therapeutic-dose anticoagulation.

Patient management

COVID-19 patients underwent mechanical ventilation if they could not maintain an arterial oxygen partial pressure to fractional inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio of less than 200 after oxygen therapy. We divided the enrolled patients into two groups: the prophylactic-dose group (from April 1, 2020 to May 20, 2020) and therapeutic-dose group (from May 21, 2020 to August 7, 2020). Patients in the prophylactic-dose group received low-molecular-weight heparin (LMWH) within the first 6 hours after ICU admission and doses of 40 mg (i.e., 4000 U) of enoxaparin twice daily. Patients in the therapeutic-dose group received

unfractionated heparin (UFH) within the first 6 hours after ICU admission, and their activated partial thromboplastin time was monitored and maintained at 1.5 to 2.5 times as the control.

Data collection

The following data were collected retrospectively from medical records: age; sex; the day from illness onset to the administration of mechanical ventilation; history of taking anticoagulant and/or antiplatelet therapy; smoking history; Charlson Comorbidity Index score [12]; the administration of ECMO; the administration of favipiravir, tocilizumab, and/or nafamostat mesylate as a treatment option for COVID-19; and status on hospital discharge (i.e., dead or alive). The date of disease onset was defined as the day when symptoms were noticed. The length of ventilation and ICU stay of each patient were also recorded. Furthermore, we collected laboratory results such as D-dimer level, fibrin-fibrinogen degradation products, and C-reactive protein levels. All blood samples were obtained after the use of mechanical ventilation and before receiving anticoagulation therapy. For all included patients, the worst values of the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology and Chronic Health Evaluation (APACHE) II scores were assessed within the first 24 hours of intubation.

Definitions and outcome measures

We defined the primary efficacy endpoint as in-hospital mortality. Furthermore, the primary safety endpoints included anticoagulation therapy-related adverse events, which were any of the following events: (1) hemoglobin level < 7 g/dL and any red blood cell transfusion within 48 hours, (2) at least two units of red blood cell transfusion within 48 hours, or (3) a clinical diagnosis of major bleeding. We defined the secondary endpoints as the administration of ECMO, ventilator-free days (VFD) 28 days after admission, ICU-free days of 28 days after admission, and the development of multiple organ dysfunction syndrome (MODS). MODS was defined as a SOFA score of ≥ 2 points in ≥ 2 organ systems [13]. Severe COVID-19 pneumonia was defined as an acute need for invasive mechanical ventilation.

Statistical analysis

In univariate analysis, continuous variables were compared using the Student's t-test or Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. All statistical analyses were conducted using R software (version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria). Two-sided *p* values < 0.05 were statistically significant.

Results

The patient selection diagram is shown in Fig. 1. One hundred fifty-one patients with COVID-19 were identified, among whom 61 patients with severe pneumonia were admitted to the ICU. Fourteen of these patients were excluded, based on the exclusion criteria. The remaining 47 patients were analyzed. Among these 47 patients, 26 (55.3%) patients were treated with heparin at a therapeutic dose. The main clinical characteristics, the laboratory data at ICU admission, the worst clinical scores during the first 24 hours after intubation, and the administered drugs are summarized in Table 1. The patients' severity scores

were not significantly different between the two groups, although the severity scores tended to be higher in the therapeutic-dose group. Favipiravir was administered to all patients. Table 2 presents the results of the univariate analysis for the study endpoints between the prophylactic and therapeutic-dose groups. A trend toward decreased in-hospital mortality occurred in the therapeutic-dose group, compared to the prophylactic-dose group, although the difference was not statistically significant [0 (0.0%) patients vs. 4 (19.0%) patients; $p = 0.067$]. We did not observe any hemorrhagic events. Compared to the prophylactic-dose group, the therapeutic-dose group had significantly more ICU-free days (median [interquartile range (IQR)]: 5 days [0–13] vs. 15 days [13–18]; $p = 0.014$). Compared to the prophylactic-dose group, the therapeutic-dose group tended to have more VFD and lower rates of ECMO therapy and developing MODS; however, the difference was not statistically significant.

Table1: Comparison of characteristics and laboratory data between the prophylactic and therapeutic-dose groups at ICU admission				
Characteristic				
	All patients (n=47)	Prophylactic-dose group (n= 21)	Therapeutic-dose group (n=26)	<i>p</i> value
Age (y), median [IQR]	57 [52-72]	55 [52-65]	62 [54-74]	0.466
Male, n (%)	45 (95.7)	21 (100.0)	24 (92.3)	1
Charlson Comorbidity Index score, median [IQR]	3 [3-4]	3 [2-4]	3 [2-4]	0.453
History of smoking, n (%)	22 (46.8)	11 (52.3)	11 (42.3)	0.595
History of anticoagulant and/or antiplatelet therapy, n (%)	12 (25.5)	5 (23.8)	7 (26.9)	1
Laboratory data				
D-dimer level, median [IQR]	2.5 [1.2-6.4]	2.1 [1.3-6.1]	3.7 [2.4-7.5]	0.118
Fibrin-fibrinogen degradation products, median [IQR]	6.6 [5.8-9.1]	6.0 [4.3-8.3]	7.2 [6.1-10.5]	0.261
C-reactive protein level, median [IQR]	10.8 [5.9-20.0]	9.1 [5.9-13.5]	14.3 [7.3-20.4]	0.370
Clinical scores				
SOFA score, median [IQR]	5 [3-5]	4 [3-5]	5 [3-5]	0.318
APACHE II score, median [IQR]	14 [11-15]	12 [11-15]	15 [12-15]	0.558
Treatment option				
Favipiravir, n (%)	47 (100.0)	21 (100.0)	26(100.0)	1
Tocilizumab, n (%)	18 (38.3)	8 (38.0)	10 (38.5)	0.328
Nafamostat mesylate, n (%)	13 (27.7)	6 (28.6)	7 (26.9)	0.314
ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation				

Table 2: The treatment outcomes of both groups				
	All patients (n=47)	Prophylactic-dose group (n=21)	Therapeutic-dose group (n=26)	<i>p</i> value
Primary outcome				
In-hospital mortality, n (%)	4 (8.5)	4 (19.0)	0 (0)	0.063
Adverse events, n (%)	0 (0)	0 (0)	0 (0)	1
Secondary outcomes				
ECMO, n (%)	6 (12.8)	5 (23.8)	1 (3.8)	0.093
VFD, median days [IQR]	18 [9-20]	14 [0-20]	18 [17-21]	0.120
ICU-free days, median days [IQR]	15 [0-17]	5 [0-13]	15 [13-18]	0.014
MODS, n (%)	10 (21.3)	7 (33.3)	3 (11.5)	0.131
IQR, interquartile range; ECMO, extracorporeal membrane oxygenation; VFD, ventilator-free days; ICU, intensive care unit; MODS, multiple organ dysfunction syndrome				

Discussion

In this retrospective historical control study, we evaluated the effects of anticoagulation therapy using a therapeutic dose of UFH on the outcomes in 47 patients with COVID-19 pneumonia requiring mechanical ventilation. We found no significant difference for any outcome, except for ICU-free days, although we found a lower in-hospital mortality and greater number of VFD and ICU-free days in the therapeutic-dose group than in the prophylactic-dose group.

Approximately 5–15% of patients with COVID-19 pneumonia require intensive care and ventilatory support [14]. The outcome of severe patients with COVID-19 requiring mechanical ventilation has been reported as extremely poor. For instance, 88% of these patients in the United States [15] and 53% of these patients in Germany [16] died. In contrast to the findings of previous reports [15, 16], although all patients in our cohort were mechanically ventilated, we demonstrated lower mortality rates among the reviewed patients (8.5%, 4/47). Of note, all patients treated with a therapeutic dose of heparin survived.

In addition to the known primary anticoagulant properties of heparin, it has therapeutic value in patients with severe lung inflammation and impaired pulmonary gas exchange [17, 18]. Anticoagulation therapy using heparin may have positive effects on the outcomes of patients with severe COVID-19 from the perspective of the effect of abnormalities in coagulation and inflammation. A previous pathological study [19] reported a high incidence of pulmonary microthrombosis in patients with COVID-19 pneumonia.

Furthermore, small pulmonary arterial thrombi were reported to be nine times more prevalent than patients with influenza [20]. In addition, despite the use of standard prophylactic anticoagulation therapy, a high incidence of thrombotic complications such as pulmonary thromboembolism (PE) [21] or arterial thrombosis [7] in patients with COVID-19 infection have been reported. UFH and LMWH inactivate several coagulation enzymes by binding to antithrombin (AT), although LMWH has a lower affinity for binding to proteins other than AT [22]. Given the clinical and pathological findings of widespread pulmonary microvascular thrombosis and thrombotic events, prophylactic dose anticoagulation using LMWH may be insufficient for patients with severe COVID-19 pneumonia and a hypercoagulable state. This emerging hypothesis has major therapeutic implications for patients with COVID-19. The possible explanation for the relatively favorable outcome in the therapeutic anticoagulation group in the present study may be related to the effect of UFH itself, in addition to the dose of heparin.

Another interesting therapeutic characteristic of heparin is its antiviral effect. Heparin inhibits infection in experimental vero cells injected with sputum from patients with severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) infection [23]. However, the mechanism and the affecting point of heparin in patients with COVID-19 remains unclear. Further basic studies are needed to reveal the role of heparin in patients with severe COVID-19.

Several limitations should be considered when interpreting our results. First, this study was retrospective with a limited sample size; thus, the risks of residual confounding and type II error exist. Additional work is necessary to provide more definitive data, including large-scale studies adjusted by covariates. Second, treatment group allocation was not based on a randomized assignment. The design of the historical cohort study was prone to potential biases, owing to the possible improvements in the management skills of severe COVID-19 pneumonia due to an increase in the experience of medical staff. Third, all patients reviewed in this study were Japanese, which limited the generalizability of the results. Race and ethnicity have major effects on coagulability and thrombotic risk [24]. Finally, patients who had already received anticoagulant and/or antiplatelet therapy were excluded from this study. The proportions were similar between the two groups in our study, although these agents could influence the coagulable state and heparin sensitivity.

Despite these limitations, we initially showed an association between the administration of a therapeutic dose of heparin and the trend of favorable outcomes in patients with severe COVID-19 requiring mechanical ventilation. This finding implicated the previous view of a potentially effective strategy in treating these patients.

Conclusion

The results of this study suggested that anticoagulant therapy using UFH at therapeutic doses may be beneficial for patients with severe COVID-19 pneumonia requiring mechanical ventilation. Further large studies are necessary to validate our results.

Abbreviations

COVID-19

coronavirus disease 2019; ICU:intensive care unit; ECMO:extracorporeal membrane oxygenation; VFD:ventilator-free day; IQR:interquartile range; RRT:renal replacement therapy; LMWF:low-molecular-weight heparin; UFH:unfractionated heparin; SOFA:Sequential Organ Failure Assessment; MODS:multiple organ dysfunction syndrome.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Tokyo Medical and Dental University. This study complied with the principles of the 1964 Declaration of Helsinki in reviewing and publishing information from the patient's medical record.

Consent for publication

Written informed consent was obtained from the patients for the publication.

Availability of data and material

The datasets analyzed in this study are not publicly available due to privacy issues, but are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

Wataru Takayama, Akira Endo, and Yasuhiro Otomo participated in the study conception and design, data collection, and drafting of the manuscript. All the authors have read the manuscript and approved this submission.

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Figures

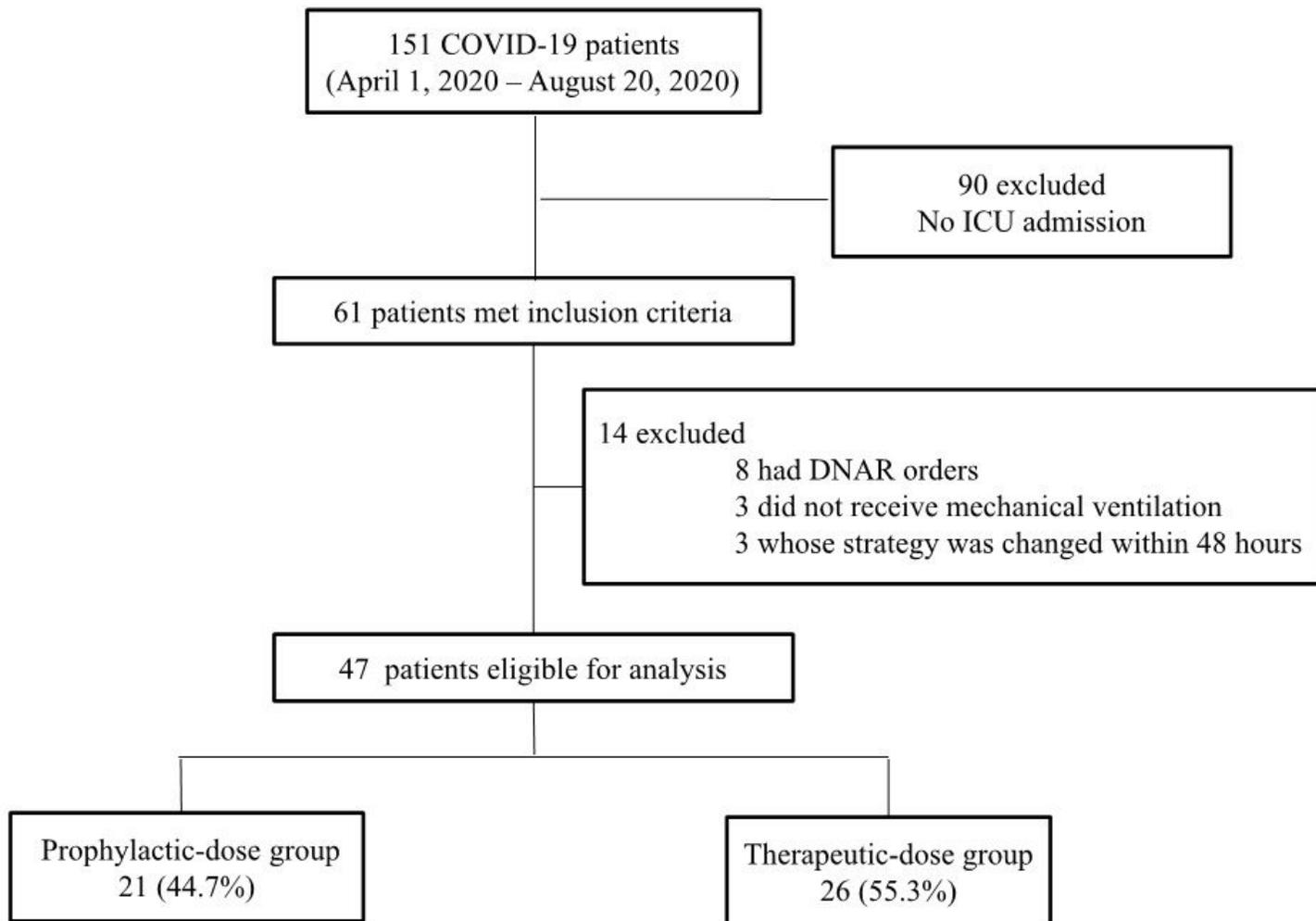


Figure 1: Patient flow diagram

ICU, intensive care unit; DNAR, do-not-attempt-resuscitation

Figure 1

ICU, intensive care unit, DNR, do not attempt resuscitation