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Comparing Therapeutic versus Prophylactic Enoxaparin Therapy in Severe COVID-19 Patients: A Randomized Clinical Trial

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has been associated with a hypercoagulopathy state; however, the efficacy of different anticoagulant regimens in preventing thrombotic events is not clear. We aimed to compare therapeutic versus prophylactic enoxaparin therapy in severe COVID-19 patients.

Methods: In this single-center, open-label, randomized controlled trial, adult patients with severe COVID-19 presentations and an increased D-dimer level of more than 4 times the normal upper limit were randomly assigned to receive either prophylactic or therapeutic dose of enoxaparin. All patients were observed for at least 4 months regarding the overall survival as the primary outcome. Hospitalization duration, the need for intensive care unit (ICU) admission, the need for mechanical ventilation, and major adverse events (MAEs) were also analyzed as the secondary outcomes. Survival analysis was done via Kaplan-Meier curves and the Log-rank test. Cox regression was used, adjusting for baseline variables.

Results: Overall, 237 patients (152 men and 85 women) were randomized to either arm (121 to prophylactic and 116 to therapeutic groups). The mortality rate was 27 (22.3%) and 52 (44.8%) in prophylactic and therapeutic arms, respectively. Prophylactic enoxaparin was associated with better survival in the log-rank test ($P < 0.001$; HR, 0.42). Additionally, a significantly lower rate of ICU admission, a lower rate of MAEs, and shorter hospitalization were observed in the prophylactic arm ($P < 0.001$, $P = 0.009$, and $P = 0.028$, respectively).

Conclusion: The results of the current study were in favor of anticoagulant treatment with prophylactic doses of enoxaparin. Still, due to the limitations of this paper, we suggest that these findings be treated cautiously.

Keywords: COVID-19, Enoxaparin, Survival

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-

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↑What is "already known" in this topic:
It is well-known that COVID-19 patients are at a higher risk for thromboembolic events and that anticoagulant agents such as low molecular weight heparin and enoxaparin are commonly used for prophylactic purposes in hospitalized patients to prevent such events.

→What this article adds:
This study suggests that prophylactic doses of enoxaparin are effective in improving overall survival in severe COVID-19 patients, as well as reducing the risk of major adverse events and shortening hospitalization duration.

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Cov-2) infection (1). The global COVID-19 incidence rate and the number of deaths are 468 million and 6.07 million, respectively, at the time of writing this paper (2). Several effective vaccinations programs, along with various protocols and drug regimens, have been designed to combat the virus and have yielded certain degrees of success. Different clinical presentations have been reported ranging from fatigue, fever, and dyspnea to acute respiratory distress syndrome, thromboembolic events, cardiovascular arrest, and death (3-5).

COVID-19 causes immune system disruption and a hypercoagulopathy state (6). The disease is related to vasculitis and microthrombi formation (7). It has been shown that thromboembolic events, like deep vein thrombosis, pulmonary thromboembolism, and venous thromboembolism, are more prevalent in patients with COVID-19 (8). Anticoagulant agents (eg, low molecular weight heparin, fondaparinux, and enoxaparin) are commonly used for prophylactic purposes in hospitalized patients (8). Treatment with low molecular weight heparin has a correlation with decreased thrombotic complications and lower mortality rates in patients with COVID-19. These effects did not increase adverse events, especially bleeding in the treated patients (9).

This study was conducted to fill up the knowledge gaps regarding the effects of anticoagulants and the correlation between the hypercoagulopathy condition and a bad prognosis in COVID-19 patients. The aim of the present study was to investigate the efficacy of treatment with different doses of an anticoagulant agent in patients with severe COVID-19.

Methods

Study Design

This randomized, controlled, open-label trial was conducted between May 2022 and September 2022 in Sina hospital, Tehran, Iran. Patients hospitalized with a COVID-19 diagnosis, confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR), were randomized to receive enoxaparin with either prophylactic or therapeutic dosage as an anticoagulant therapy. The study protocol was registered in the Iranian Registry of Clinical Trials (IRCT20220412054515N1). The study was performed in accordance with the declaration of Helsinki, and the ethical board of Tehran University of Medical Sciences approved this trial (IR.TUMS.SINAHOSPITAL.REC.1401.013). Patients or their representatives gave written informed consent before randomization.

Participants

Patients over 18 years with an RT-PCR confirmed COVID-19 diagnosis and severe clinical presentations that required hospitalization were eligible for inclusion if they had increased D-dimer levels >4 times the normal upper limit. Severe COVID-19 infection was defined as the occurrence of 2 of the following factors: (1) respiratory rate >30 times/minute; (2) Spo2 of <93%; (3) Pao2/Fio2 <300 mmHg; and (4) rapid progression (>50%) on computed tomography (CT) scan imaging over 24 to 48 hours (10). The exclusion criteria included pregnancy, history of cerebrovascular accident (CVA) in the past month, history of major surgery in the past 2 weeks, history of heparin-induced thrombocytopenia, other definitive indications for therapeutic anticoagulant treatment, and enoxaparin contraindications—such as active bleeding or severe thrombocytopenia.

Sample Size Calculation

The minimum sample size needed for each group to detect whether the stated difference exists between the 2 proportions was calculated to be 79 in each group based on a previously published (11) randomized trial using a well-known formula (12) and the calculator website (13) (https://select-statistics.co.uk/calculators/sample-size-calculator-population-proportion/)

This calculator uses the following formula for the sample size:

$n = N*X / (X + N - 1)$,

where $X = Z_{\alpha/2}^2 *p*(1-p) / MOE^2$, and $Z_{\alpha/2}$ is the critical value of the normal distribution at $\alpha/2$ (eg, for a 95% CI, α is 0.05 and the critical value is 1.96), MOE is the margin of error, p is the sample proportion, and N is the population size. Note that the Finite Population Correction has been applied to the sample size formula.

We used a power of 90% and an alpha error of 5%. A previous study have suggested a summation sample size of 347 in both prophylactic and treatment doses. However, in light of potential differences in COVID-19 strains, disease severity, and attrition, we adjusted the sample size calculation. We also considered that newer strains (14) or different regions of COVID-19 virus(15) may have been shown to have lower mortality rates than earlier strains, which could impact the study results. Therefore, we arrived at a final sample size of 124 per group by consensus. During the study, we randomized a total of 248 patients to account for possible missing data or withdrawals of consent.

Randomization and Procedure

Patients were randomized in a 1 to 1 ratio using block randomization with a random block size of 4 to 8 using a computer-generated random allocation algorithm to either receive a prophylactic or therapeutic dosage of enoxaparin. Patients and researchers were not blinded to the group assignments after the allocations. Prophylactic treatment patients received daily subcutaneous doses of 40 mg enoxaparin, and if they had a body mass index (BMI) >40 kg/m^2, the 40 mg doses of enoxaparin were administered 2 daily. Patients in the therapeutic group were subjected to subcutaneous 1mg/kg enoxaparin twice a day. In cases of patients with chronic kidney disease (CKD) with a glomerular filtration rate >30 mL/min, the administered dosage was reduced to 1mg/kg once daily in the treatment arm and 30 mg daily in the prophylactic arm. Enoxaparin treatment in both groups was continued until death or discharge from the hospital.

Outcomes

The primary outcome of this study was all-cause mortal-

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ity and overall survival. All patients were observed for at least 4 months after discharge. Secondary outcome measures were hospitalization duration, the need for intensive care unit (ICU) admission, and the need for mechanical ventilation. Major adverse events (MAEs) were analyzed as the safety outcome. MAEs included major bleedings as defined by International Society on Thrombosis and Haemostasias criteria (16).

Statistical Analysis

The data were analyzed using SPSS software. Demographic and baseline data were collected and compared between study arms. Categorical variables were reported as sums and percentages and were compared using the chi-square test and the Fisher exact test. Normal distribution of continuous variables was assessed using the Shapiro-Wilk test. Independent sample t tests and the Mann-Whitney U test were used for comparison of continuous variables with normal and nonnormal distribution, respectively, and they were reported as means and standard deviations or medians and interquartile ranges. Kaplan-Meier curves were utilized for survival analysis, and the Log-rank test was used to test the equality of treatment groups. The Cox regression analysis was used to assess the effects of baseline variables. The following baseline variables were adjusted: age, sex, BMI, underlying conditions (diabetes, hypertension, cardiac disease, cancer, pulmonary diseases, CKD, CVA, and cirrhosis), admission variables (SBP, HR, temp, O2 sat, platelet count, quantitative CRP, D dimer, and onset to admission time), and finally the associations were reported as hazard ratio (HR) (Table 1).

Only the patients who completed the study were assessed, and all outcomes were examined according to the protocol population. For all tests, the significance level was set at 5%.

Results

Patients

Participants were enrolled between May 2022 and September 2022 from Sina hospital. Overall, 237 patients (152 men and 85 women), with a mean age of 60.5 ± 15.85 years met the inclusion criteria and were accounted for in the final analysis. A total of 121 patients were assigned to receive prophylactic enoxaparin doses, while the other 116 patients received therapeutic dosages—8 and 3 patients withdrew their consent, respectively, and no other patients dropped out of the study. The details of patient selection and randomization is demonstrated in Figure 1. The baseline characteristics of study groups were compared and summarized in Table 1, and no significant difference was observed in this regard.

Outcomes

At the end of the follow-up, a sum of 79 patients had died in both treatment arms. The Kaplan-Meier curve for

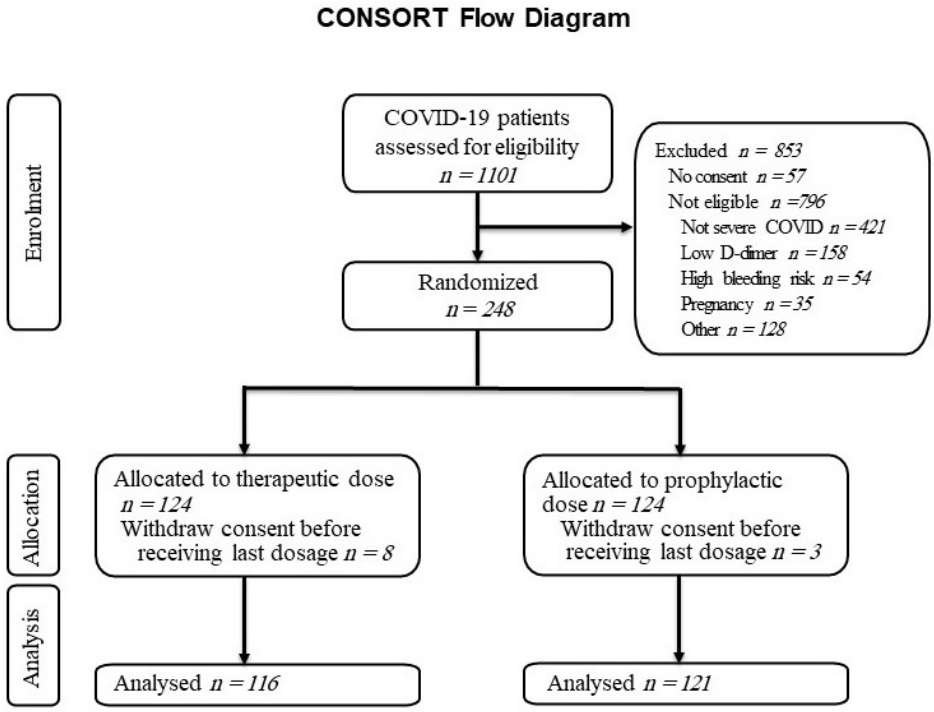

Figure 1. CONSORT Flow Diagram

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Table 1. Baseline characteristics of study groups

Characteristic	Prophylactic dose (n=121)	Therapeutic dose (n=116)	*P* value	HR
Age: mean (SD)	60.0 (15.2)	61.1 (16.4)	<0.001	1.03 (1.02 – 1.05)
Gender: no. (%)				
Female	38 (32%)	47 (41%)	0.860	1.04 (0.66 – 1.64)
Male	83 (68%)	69 (59%)		
BMI: median (IQR)	26.6 (5.5)	26.5 (6.1)	0.290	0.96 (0.90 – 1.03)
Underlying conditions: no. (%)				
Diabetes	48 (39%)	38 (32%)	0.280	1.27 (0.81 – 2.00)
Hypertension	56 (46%)	65 (56%)	0.230	1.31 (0.83 – 2.05)
Cardiac disease	34 (28%)	38 (32%)	0.630	1.12 (0.70 – 1.78)
Cancer	6 (5%)	9 (7%)	0.000	3.30 (1.74 – 6.25)
Pulmonary diseases	8 (6%)	11 (9%)	0.280	1.45 (0.72 – 2.92)
CKD	9 (7%)	7 (6%)	0.340	1.45 (0.66 – 3.15)
CVA	4 (3%)	6 (5%)	0.050	2.27 (0.98 – 5.22)
Cirrhosis	1(<1%)	0 (0%)	0.020	9.67 (1.29 – 72.31)
Admission variables				
SBP: mean (SD)	126.5 (23.4)	130.8 (25.9)	0.010	0.98 (0.97 – 0.99)
HR: mean (SD)	89.3 (15.4)	91.2 (16.7)	0.810	1.00 (0.98 – 1.01)
Temp: mean (SD)	37.2 (0.85)	37.2 (0.88)	0.550	0.91 (0.66 – 1.22)
O2 sat: mean (SD)	88.1 (8.2)	87.8 (9.3)	0.000	0.96 (0.95 – 0.98)
Platelet count (10^9/L): median (IQR)	194.0 (127.2)	206.5 (153.0)	0.260	0.99 (0.99 – 1.00)
Quantitative CRP: median (IQR)	53.0 (67.5)	89.5 (58.4)	<0.001	1.00 (1.00 – 1.01)
D dimer: median (IQR)	1907 (4261)	2056 (4084)	<0.001	1.00 (1.00 – 1.00)
Onset to admission time: median (IQR)	7 (7)	6 (5.5)	0.350	0.95 (0.82 – 1.05)

SD: standard deviation, IQR: interquartile range, CKD: chronic kidney disease, CVA: cerebrovascular accident, SBP: systolic blood pressure, HR: heart rate, Temp: temperature

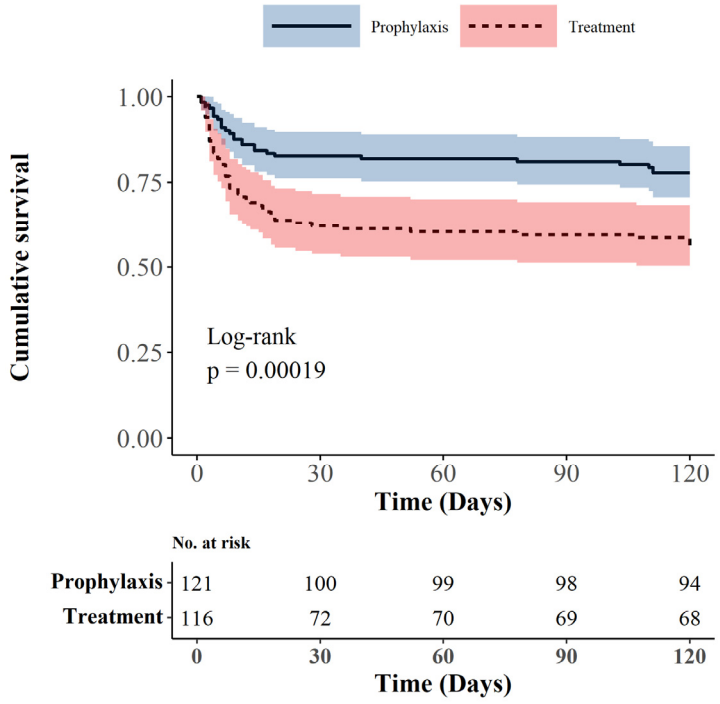

Figure 2. Kaplan-Meier curve of overall survival for prophylactic and therapeutic groups

overall survival in Figure 2 shows that prophylactic enoxaparin was linked to improved outcomes—mean survival days, 99.12 ± 3.89 vs 75.65 ± 5.08 for prophylactic and therapeutic dose, respectively. In the log-rank test, a significant difference between groups was observed (x^2=13.94, P = 0.005). The HR calculated by the Cox regression model is demonstrated in Tables. In addition, the baseline variables reported in Table 1 were assessed for any predictive value for overall survival using Cox regression. Systolic blood pressure, D dimer level, and presence of underlying cirrhosis proved significant in this regard (P = 0.010, P < 0.001 and P = 0.020, respectively). However, it is noteworthy to mention that only one of the patients had concurrent cirrhosis. The analysis demonstrated a mortality HR of 0.98 (0.97-0.99) for each unit increase in systolic blood pressure, an HR of 1 for each unit increase

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Table 2. Outcomes measures

Outcome	Prophylactic dose (n=121)	Therapeutic dose (n=116)	Hazard ratio (HR) / Relative Risk / Mean difference (MD)	*P* value
Primary outcome				
Overall mortality: no. (%)	27 (22.3%)	52 (44.8%)	HR 0.42 (0.26 – 0.67)	<0.001
Secondary outcomes				
Hospitalization duration: mean (SD)	6.43 (5.98)	8.19 (6.26)	MD -1.76 (-3.32 – -0.19)	0.028
ICU admission: no. (%)	20 (16.5%)	44 (37.9%)	RR 0.43 (0.27 – 0.69)	<0.001
Mechanical ventilation: no. (%)	16 (13.2%)	25 (21.6%)	RR 0.61 (0.34 – 1.08)	0.090
MAEs: no. (%)	85 (70.2%)	98 (84.5%)	RR 0.83 (0.72 – 0.95)	0.009

in D dimer level, and an HR of 19.75 (2.55-153.03) for underlying cirrhosis.

Hospitalization duration was compared between the groups, which was significantly higher in the therapeutic enoxaparin group with a mean difference of 1.76 (P = 0.028). The need for ICU admission was also significantly higher in the therapeutic dosage group (P < 0.001). However, the need for mechanical ventilation was comparable between both groups (P = 0.090). In addition, analysis of MAEs demonstrated that prophylactic enoxaparin dosage was associated with better safety with a relative risk of 0.83 (P = 0.009) (Table 2).

Discussion

In this controlled, open-label trial, we randomly divided the hospitalized patients with COVID-19 into 2 groups. One group received enoxaparin with therapeutic dosages, and the other group was assigned to take enoxaparin with prophylactic doses. We found that prophylactic enoxaparin was related to better overall survival results. Furthermore, higher hospitalization duration and a higher need for ICU admission were seen in the therapeutic group. Prophylactic doses of enoxaparin were safer than therapeutic doses regarding MAEs. The present study rejected the hypothesis that the treatment with therapeutic dosages of anticoagulant could yield better outcomes in patients with COVID-19.

There are several articles assessing clinical outcomes of anticoagulant with therapeutic doses in hospitalized patients with COVID-19. Nevertheless, to the best of our knowledge, this is the first trial showing prophylactic regimen's superiority. Canoglu et al conducted a retrospective cohort study and evaluated 154 patients with moderate COVID-19 treated with either prophylactic or therapeutic doses of enoxaparin. They showed that the therapeutic dosage of enoxaparin reduces the mortality rate (17). A total of 278 consecutive patients with mild COVID-19 were included in another cohort research conducted by Martinelli et al. Likewise, their study showed that the mortality rate, clinical deterioration, and venous thromboembolism were lower in those who were treated with therapeutic enoxaparin dosages (18). Trinh et al investigated severe cases of COVID-19 in a cohort manner. Their results also proposed the effectiveness of therapeutic doses of anticoagulation in reducing the mortality rate. They found that bleeding was comparable between the 2 groups (19). There are also other surveys on the effects of anticoagulants other than enoxaparin, which yielded various results (20-22). In a systematic review and meta-analysis performed by Yasuda et al, it was shown that the anticoagulant treatment with prophylactic doses and therapeutic doses both decrease the risk of short-term mortality and venous thromboembolism compared with no anticoagulant treatment. They also concluded that the mortality rate was similar in both groups. In addition, therapeutic dosages declined venous thromboembolism rates but induced bleeding (23). The results of the present study were against this review and showed that the prophylactic dosages of anticoagulant treatment are superior to therapeutic dosages regarding survival. This discrepancy might be explained considering that, as opposed to our study, multiple anticoagulant drugs were analyzed in the mentioned systematic review and no COVID-19 severity limit was implemented.

Limitations

This study encountered some drawbacks. The study was not double-blind, which could negatively affect our results. In addition, the study has a relatively small sample size, which decreases the power of the research and the generalizability of the data. We only assessed the effects of enoxaparin; therefore, it was not possible for us to discuss other anticoagulants. We suggest performing further trials to overcome these limitations before reaching a firm conclusion.

Conclusion

The results of the present study were in favor of anticoagulant treatment with prophylactic doses of enoxaparin. However, given the limitations of this study, we advise that these results be interpreted with caution. Before making a solid decision, we also advise conducting more trials. Our study rigorously evaluated treatment effectiveness using the per protocol population, aligning with real-world conditions of treatment adherence. Given the significance of sensitivity analysis in certain contexts, we suggest that future studies or particular cases call for taking the intention-to-treat population into account for a more comprehensive assessment, strengthening the validity of our results.

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by M.A.SH., A.H.N., D.J., and M.M. The first draft of the manuscript was written by MR.F. and S.K. (contributed as first authors), and all other authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethics Guidelines

The study was performed in accordance with the declaration of Helsinki, and the ethical board of Tehran University of Medical Sciences (IR.TUMS.SINAHOSPITAL.REC.1401.013). Patients or their representatives gave written informed consent before randomization.

Conflict of Interests

The authors declare that they have no competing interests.

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