ORIGINAL ARTICLE

CONTENTS

Effect of Enoxaparin on D-dimer levels in hospitalized Corona Virus patients with a comparison of its level in patients with comorbid conditions

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ABSTRACT

Aim: The main goal is to assess the levels of comorbid diseases and examine the changes in D-dimer in hospitalized patients before and following SC enoxaparin medication.

Material and Methods: At the Al-Yarmouk Teaching Hospital in Baghdad, Iraq, from October 2022 to May 2023, 86 patients who were hospitalized and had severe to critical COVID-19 infections provided data for a retrospective analysis.

Results: The medical records of all COVID-19 patients who were hospitalized and whose D-dimer level was greater than 0.5 mg/l and who were given enoxaparin (40 mg subcutaneously) were reviewed with the requisite authorization from the relevant authorities. The D-dimer level was assessed following therapy on the day of admission and day five after commencing enoxaparin. An examination of 86 case records revealed that persons with COVID-19 had significantly decreased D-dimer levels after taking subcutaneous enoxaparin (p-value<0.0001). The comorbidities (diabetes mellitus, hypertension) of patients who received the drug were compared.

Conclusions: Enoxaparin and other anticoagulants were utilized to treat the coagulopathy brought on by COVID-19. Low molecular weight heparin enoxaparin has demonstrated positive outcomes in the management of VTE. A decrease in D-dimer level is anticipated when COVID-19 patients are treated with subcutaneous enoxaparin, partly because decreased coagulation results in lower fibrin formation.

KEY WORDS: COVID-19, enoxaparin, D-dimer, venous thromboembolism, diabetes mellitus, hypertension

Wiad Lek. 2024;77(4):828-833. doi: 10.36740/WLek202404131 DOI

INTRODUCTION

COVID-19, which was identified as a pandemic by WHO in March 2020, presents a serious threat to global health. Several coagulation problems, including venous thromboembolism (VTE), is thought to be linked to COVID-19, according to a recent literature review [1, 2]. Leukopenia, lymphopenia, elevated levels of lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, and aminotransferase are among the laboratory results [3]. It also causes difficulties with the heart, hematology, kidneys, and other systems. Patients with COVID-19 experience thromboembolic events, with critically sick patients at the highest risk, where Between 25 and 53 percent of COVID-19 hospitalized patients experience thrombosis [4]. A rise in the Padua prediction score of >4 associated with infection with COVID-19 has been observed 40 percent of patients. A score >4 indicates a higher risk of venous thromboembolism (VTE), and the Padua score was developed to predict VTE risk in hospitalized medical patients. Endothelial dysfunction, hypercoagulable state, and stasis-the three components of Virchow's triad-are all made worse by COVID-19 infection. It makes thrombosis and endothelial dysfunction more likely, which is brought on by ACE2 and leads to an increase in D-dimer, fibrin, and fibrinogen. Prothrombin time, activated partial thromboplastin time, and thrombin time are also impacted and appear to be longer [5, 6]. In these patients, elevated D-dimer readings have been associated with poor prognosis and increased mortality [7]. People with numerous co-morbid conditions, such as diabetes, hypertension, and hypothyroidism, frequently have elevated D-dimers and higher death rates [8]. Low molecular weight heparin enoxaparin has demonstrated positive outcomes in the treatment and prevention of VTE, lowering the risk of mortality. It activates ant thrombin to produce

an anticoagulant action. A decrease in D-dimer level is anticipated when COVID-19 patients are treated with subcutaneous enoxaparin, partly because decreased coagulation results in lower fibrin formation. In light of the foregoing, research is being planned to determine how enoxaparin affects D-dimer levels [9]. Model WHO Lists of Essential Drugs includes enoxaparin, which has the benefit of a daily dose and a recommended standard thrombi prophylaxis duration until hospital release. Clinicians must to be knowledgeable about the elevated risk of bleeding if the therapeutic dose is administered. This risk includes substantial hemorrhage requiring transfusion (gastrointestinal, for example) as well as clinically significant bleeding even in the absence of transfusion (intracranial, for example). Patients should obtain baseline values for Prothrombin time or the international normalized ratio, partial thromboplastin time, platelet count and creatinine before starting therapeutic or intermediate-intensity anticoagulation [10].

AIM

The main goal is to assess the levels of comorbid diseases and examine the changes in D-dimer in hospitalized patients before and following SC enoxaparin medication.

MATERIAL AND METHODS

PATIENTS AND STUDY DESIGN

Data for this observational retrospective study were taken from the case notes of patients hospitalized in a hospital with a focus on COVID-19.

INCLUSION CRITERIA

With at least two measurements for the D-dimer (the first one before receiving the treatments and the second one on the last day of receiving the treatments), hospitalized patients with COVID-19 infection and D-Dimer level >0.5 mg/l, age of at least 18 years, being free of pregnancy, and having taken an injectable anticoagulant for at least three days. Patients who did not meet these requirements were not included in the trial. The study was carried out between October 2022 and May 2023. 86 patients made up the sample.

EXCLUSION STANDARDS

- Disorder of Bleeding (cirrhosis, hemorrhagic stroke within a year, malignancy and so on)
- Thrombocytopenia (100 109/L)
- Severe Anemia (Hemoglobin less than 8 g/dl)
- Abnormalities in coagulation
- DVT or pulmonary embolism; previous heparin-induced thrombocytopenia; antiplatelet therapy

DATA COLLECTION

With proper authorization from the appropriate authorities, characteristics of the patient, including age, sex, and the presence of another disease (such as HT, and DM), were retrieved from the medical records department. Hospitalized COVID-19 patients' D-dimer levels were documented within 24 hours of their hospitalization, and alters were assessed 120 hours after therapy with SC enoxaparin.

STUDY SETTING AND ETHICAL APPROVAL

The study was carried out at Al-Yarmouk Teaching Hospital in Baghdad, Iraq, from October 2022 to May 2023 with the Department of Pharmacy at Al-Maarif University College's clearance.

STATISTICAL ANALYSIS

The statistical analysis for this study was completed using a Microsoft Excel spreadsheet was used to gather, compile, and evaluate all of the data. Conduct extra statistical analysis to assess the outcomes of treatments. The Statistical Package for the Social Sciences (SPSS), version 24, was used. P values less than 0.05 are considered significant. Numerical data were described using the mean, and standard deviation. An independent student T-test was used to compare the effects of the therapies on the indicator as an average change in the number per patient per day. The null hypothesis was tested, and the p-values were used to assess the significance of the testing. A p-value of less than 0.05 was used to determine if a result was significant.

RESULTS

To determine if gender and age had an impact on the D-dimer, the typical baseline D-dimer value was determined in consideration of the demographic variances. Males had greater D-dimer baseline averages than females before to treatment, yet the distinction was not statistically meaningful P-value > 0.05. Individuals under 60 years old had greater D-dimer baseline averages than individuals over 60. The average age difference was a sizable disparity (Table 1).

Table 1. Baseline D-dimer average by age, gender (male, female)

Demography	D-dimer mg/L	SDV mg/L	Number of patients	P-value
Gender				
Male	2559.87	±3275.719	56	0.6
Female	2463.11	±2204.845	30	
Age				
≥60 years	3267.32	±3604.521	53	0.03
<60 years	1864.05	±1778.583	33	

Table 2. D-dimer baseline average for COVID-19-infected hospitalized patients before and after enoxaparin treatment

General	D-dimer prior to therapy Mg /l	D-dimer after therapy Mg/l	P - value
patient	6.79±7.22	3.84±5.05	<0.0001

Table 3. Effect of enoxaparin use on D-DIMER before and after in general people with COVID-19 who have diabetes

Diabetes	D-dimer prior to therapy Mg /l	D-dimer after therapy Mg/l	P-value
Positive	7.3654±7.65	4.401±4.8	0.056
Negative	6.7538±6.84	3.60±5.08	<0.0001

D-dimer prior to therapy Mg /l:
Positive- mean ± SD of D-dimer level in diabetic patient before enoxaparin treatment
Negative- mean ± SD of D-dimer level in Non- diabetic patient before enoxaparin treatment
D-dimer after therapy Mg/l:
Positive- mean ± SD of D-dimer level in diabetic patient after enoxaparin treatment
Negative- mean ± SD of D-dimer level in Non- diabetic patient after enoxaparin treatment

Table 4. Effect on D-DIMER before and after enoxaparin usage among general COVID-19 patients having hypertension

Hypertension	D-dimer before treatment mg/L	D-dimer after treatment mg/L	P-value
Positive	4.8716±6.06795	2.61±4.054	0.18
Negative	7.3154±7.17541	3.87±5.261	<0.0001

D-dimer before treatment Mg /L:
Positive- mean ± SD of D-dimer level in hypertension patient before enoxaparin therapy
Negative- mean ± SD of D-dimer leDvel in hypertension patient before enoxaparin therapy
D-dimer after treatment Mg/L:
Positive- mean ± SD of D-dimer level in hypertension patient after enoxaparin therapy
Negative- mean ± SD of D-dimer level in hypertension patient after enoxaparin therapy

Anticoagulants like enoxaparin were evaluated for effectiveness using the D-dimer value. Those infected with coronavirus had their D-dimer baseline average determined both before and after using enoxaparin. Look at (Table 2).

Patients who got low molecular weight heparin (Enoxaparin) had their comorbidities (diabetes mellitus, hypertension) compared. Both Tables 3 and 4 present the analysis.

DISCUSSION

According to the results of the current investigation, patients with coronavirus disease had D-dimer levels that were above average. Numerous factors could be at play in this increase in D-dimer readings in coronavirus patients, including:

I) A disease, which may result in the release of cytokines that are pro-inflammatory and a storm of inflammation
II) Some COVID-19 patients have varying degrees of inflammation and hypoxia, which might result in thrombosis or higher oxygen requirements
III) Blood coagulation may also be impacted by severe infection or acute inflammation brought on by sepsis. D-dimer tests are therefore very helpful for identifying thrombotic conditions, which is why individuals with coronavirus were noted to be in hypercoagulable condition [11].

In the collection of information generally gathered at admission, age, and sex were very significant indicators of disease severity. With age, sexual differences become less pronounced. If disease severity was

measured using clinical markers rather than radiologic markers, age discrepancies were more significant. This study is consistent with another one where Jecko Thachil et al., 2020 demonstrated that Enoxaparin anticoagulation therapy appeared for a more favorable prognosis about mortality when coagulopathy brought on by sepsis scores were applied to clients with high levels of D-dimer of greater than six times what is considered to be normal [12]. Even though D-dimer decreases in diabetic patients after using enoxaparin (p-value=0.056), it is not statistically significant. The D-dimer concentration following and before enoxaparin revealed a considerable decrease in non-diabetic subjects (p-value 0.0001), which is extremely important. According to recent research, diabetic patients have a much higher chance of dying in hospitals from COVID-19 than individuals without impaired glucose tolerance (HR=2.36) [13]. According to Gregory et al., people with type 2 (DM2) and type 1 (DM1) diabetes are more likely than healthy people to experience a serious disease brought on by COVID-19. In this study, individuals with DM1 and DM2 had similar adjusted odds ratios (OR) for hospitalization rates (3.90 for DM1 *vs.* 3.36 for DM2) and disease severity (3.35 *vs.* 3.42) [14]. Patients with coronavirus may have increased D-dimer levels on account of thrombin production-inducing inflammation brought on by viral infections and dysfunctional endothelium cells. Higher levels of D-dimer can also occur in these people if they have a physiological state, such as pregnancy, and a concurrent ailment, such as diabetes, cancer, or a stroke [15]. D-dimer readings among hypertensive decreased after taking enoxaparin, although they did not change significantly (p-value=0.18). The D-dimer value was lower in non-hypertensive, and the significance of this group difference was determined by a p-value of 0.0001. In their study, Diana Delali, Juraj Jug, and Ingrid Prkain demonstrated that post-COVID arterial hypertension, which affects 1 in every 6 patients and is most common in women, is a true and dangerous side effect of a COVID-19 infection. The time frames given in this research are meant to help provide a framework for reasonable and sufficient follow-up patient evaluations following acute COVID-19, particularly for the time from the positive PCR test to the onset of post-COVID symptoms. This will make it possible to identify any post-COVID sequelae in a timely manner and begin treating them before they get worse [16]. Additionally, COVID-19 individuals with underlying comorbidities, such as hypertension, are linked to reduced SARS-CoV-2 viral clearance [17]. Trump et al., [18] noted that due to hypertension's aberrant immune response and airway inflammation, SARS-CoV-2 clearance is delayed and lung inflammation in COVID-19 patients is exacerbated. As a result, hypertension may worsen COVID-19 and its associated consequences by delaying SARS-CoV-2 clearance. Lippi and others [19] noted that there is the link between hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19). Dyspnea, hypertension, coronary heart disease, diabetes, male gender, advanced age and cerebrovascular illness are all linked to critical D-dimer concentrations [20]. According to the findings, patients over 60 years of age had aberrant D-dimer readings, with a P-value of 0.001 showing no effect of gender on D-dimer levels. Higher D-dimer levels have been linked to both the male and female genders in other studies [20], with women having a greater chance of contracting thrombotic disorders in the coronavirus study. In general, it appears that age and D-dimer levels are related [21]. Additionally, several research suggested that the use of enoxaparin in COVID-19 may have both anti-inflammatory and anticoagulant effects. The danger of thrombosis in important organs will therefore be reduced by beginning Enoxaparin treatment sooner [22].

CONCLUSIONS

This observational study demonstrates that individuals admitted to the hospital for COVID-19 experienced a drop in D-Dimer levels while receiving treatment with enoxaparin. Enoxaparin and other anticoagulants were utilized to treat the coagulopathy brought on by COVID-19. Low molecular weight heparin enoxaparin has demonstrated positive outcomes in the management of VTE. A decrease in D-dimer level is anticipated when COVID-19 patients are treated with subcutaneous enoxaparin, partly because decreased coagulation results in lower fibrin formation.

Since the usefulness of enoxaparin in improving clinical outcome in corona virus 2019 patients seem consistent and its use is routine in many COVID hospitals and important to evaluate its clinical efficacy in corona virus 2019 patients.

RECOMMENDATION

There is an urgent need for multi-centric trials to assess enoxaparin's clinical efficacy in COVID-19 patients because its value-enhancing clinical outcomes in patients with COVID-19 appears reliable and its usage is commonplace in numerous coronavirus institutions.

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CONFLICT OF INTEREST

The Author declare no conflict of interest

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RECEIVED: 16.09.2023
ACCEPTED: 15.03.2024