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Effect of enoxaparin on d-dimer level and survival in hospitalized COVID-19 patients: An observational study

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Abstract--Coronavirus disease 2019 (COVID-19), is caused by Severe Acute Respiratory Syndrome Coronavirus 2(SARS-CoV-2) infection. It is associated with a severe coagulopathy i.e. Venous Thromboembolism (VTE), for which optimum strategies ought to be developed for early treatment. D-dimer, a fibrin degradation product is raised in critical COVID-19 pneumonia and increases mortality. Enoxaparin, a low molecular weight heparin, has shown beneficial results in prevention and treatment of VTE. During management of COVID 19 patient with subcutaneous enoxaparin a decrease in D-dimer level is expected primarily because of decreased coagulation leading to decreased fibrin production. It was an observational study with data collected from 86 patients admitted to dedicated COVID hospital,

VIMSAR, Burla, Odisha, from April 2022 to August 2022. Medical records of all hospitalized COVID-19 patients with D-dimer $> 0.5\text{mg/l}$ and prescribed enoxaparin (40mg s.c.) were analyzed with due permission from authorities. D-dimer level was evaluated before and after treatment with enoxaparin (on day of admission and day 5). Total 86 case records were analyzed and there was significant reduction in D-dimer level in covid patients after subcutaneous enoxaparin. (z value= -5.265, p value $<.0001$). Data analysis was done in SPSS software version 21 using a Nonparametric Test i.e. Wilcoxon Signed Ranks Test. Subcutaneous Enoxaparin causes significant reduction in D-dimer level in covid patients.

Keywords---COVID-19, enoxaparin, D-dimer.

Introduction

- COVID -19 poses a major global health crisis, having been declared pandemic on 11 March, 2020 by WHO.
- Recent literature review suggests that COVID -19, is associated with several coagulation abnormalities like venous thrombo-embolism(VTE) , pulmonary embolism, stroke, myocardial infarction, micro-vascular thrombosis, acute arterial thrombosis.^{1,2}
- Coagulopathy is a poor prognostic factor and optimum strategies ought to be developed for early diagnosis, prevention and treatment of VTE in COVID- 19 patients.
- Initially, coagulopathy in COVID-19 patients presents with elevated fibrin degradation product, especially D-dimer.³
- Raised D-dimer values have indicated poor prognosis and high mortality in such patients.⁴
- Individuals with multiple co-morbidities like Diabetes mellitus, Hypertension, hypothyroidism tend to have high D-dimer and are more likely to have raised mortality.⁵
- Enoxaparin, a low molecular weight heparin, has shown beneficial results in prevention and treatment of VTE, reducing the risk of mortality. It achieves anticoagulant effect by activating antithrombin.⁶
- During management of COVID-19 patients with subcutaneous enoxaparin a decrease in D-dimer level is expected primarily because of decreased coagulation leading to decrease fibrin production.
- With this background, this study is being planned to study the effect of enoxaparin on D-dimer level.

Aims and Objectives

- Primary objective-To evaluate the changes in D-dimer before and after subcutaneous enoxaparin therapy in hospitalized patients with COVID 19
- Secondary objective -to watch for survival status of those patients after enoxaparin.

Material and Methods

Study design- It is an observational retrospective study, data collected from case sheets of patients admitted to dedicated COVID hospital, VIMSAR, BURLA. Place of study- The study conducted at COVID Hospital of VIMSAR, Burla, which is the largest tertiary care hospital of Western Odisha.

- Period of study- This study conducted from April 2022- August 2022.
- Sample size-86 patients

Statistical Analysis

- done using IBM SPSS software version 21 using Wilcoxon Signed Rank test
- p value <0.05 considered significant

Inclusion criteria

COVID-19 patients with D-DIMER LEVEL > 0.5 mg/l

Exclusion criteria

- age < 18 and > 80 years
- Bleeding Disorder (peptic ulcer, esophageal varices, cerebral aneurysm, cancer at high risk of bleeding, cirrhosis, hemorrhagic stroke less than one year)
- Thrombocytopenia (100×10^9 /L)
- Severe Anemia (Hb < 8g/dl)
- Coagulation abnormalities
- Previous heparin induced thrombocytopenia
- On antiplatelet therapy
- DVT or pulmonary embolism

Data Collection

- The patient characteristics like age, sex, gender and co-morbidities (like hypertension, diabetes mellitus) obtained from medical records section with due permission from authority.
- Study started after due approval from institutional ethical committee 043-2022/I-S-O/17/Dt.17.05.2022
- D-dimer level of hospitalized COVID-19 patient within 24 hours of hospital stay noted and changes in same evaluated after 120 hours post treatment with subcutaneous enoxaparin (dose 40 mg or 60 mg depending on body weight)
- survival status of those patients are also observed

Results and Observation

Table 1
effect on D-DIMER before and after enoxaparin usage among general covid19 patient

General patient	D-DIMER 1	D-DIMER 2	Z value	P value
Covid 19 patient	6.88±7.12	3.74±5.03***	5.265	<0.0001

D-DIMER1 - Mean ± SD of D-DIMER level(mg/lt) in patient before enoxaparin therapy

D-DIMER2 - Mean ± SD of D-DIMER level(mg/lt) in patient after enoxaparin therapy

Table 2
Effect on D-DIMER before and after enoxaparin usage among general covid19 patient having diabetes

diabetes	D-DIMER 1	D-DIMER 2	Z value	P value
yes	7.2864±7.74	4.410±4.9	1.899	0.057
No	6.7448±6.95	3.50±5.09	5.108	<0.0001

D-DIMER1 - Mean ± SD of D-DIMER level(mg/lt) in diabetic patient before enoxaparin therapy

Mean ± SD of D-DIMER level(mg/lt) in non-diabetic patient before enoxaparin therapy

D-DIMER2 - Mean ± SD of D-DIMER level(mg/lt) in diabetic patient after enoxaparin therapy-

Mean ± SD of D-DIMER level(mg/lt) in non-diabetic patient after enoxaparin therapy

Table 3
Effect on D-DIMER before and after enoxaparin usage among general covid19 patient having hypertension

hypertension	D-DIMER 1	D-DIMER 2	Z value	P value
yes	4.9615±6.07694	2.52±4.062	2.342	0.19
No	7.2256±7.27451	3.96±5.181	4.762	<0.0001

D-DIMER1 - Mean ± SD of D-DIMER level(mg/lt) in hypertensive patient before enoxaparin therapy

Mean ± SD of D-DIMER level(mg/lt) in non-hypertensive patient before enoxaparin therapy

D-DIMER2 - Mean ± SD of D-DIMER level(mg/lt) in hypertensive patient after enoxaparin therapy-

Mean ± SD of D-DIMER level(mg/lt) in non-hypertensive patient after enoxaparin therapy

Discussion

- Coagulation dysfunction in COVID -19 patients leads to severe illness and fatal outcome, is characterized by elevated D-dimer level and thrombi in veins and arteries
- Without co-morbid condition, D-dimer value reduced after enoxaparin, group difference found to be highly significant (z value 5.265 and p value<0.0001)
- This study correlates with another study in which sepsis induced coagulopathy score were to applied to patients with D-dimer level more than six fold of upper limit of normal, anticoagulation therapy with enoxaparin appears to have better prognosis in relation to mortality (32% VERSUS 52.4%,P=.017)¹³(Jecko Thachil et al,2020)⁷
- In Diabetic patient, though D-dimer is reduced after enoxaparin usage, it is not significant (z value of 1.89 ,p value = 0.057)
- In non-diabetic cases D-dimer value after and before enoxaparin showed a significant reduction (z value of 5.10 and p value <0.0001) which is highly significant.
- Among hypertensives D-dimer value reduced after usage of enoxaparin but is not significant (z value of 2.34, p value = 0.19)
- In non-hypertensives D-dimer value reduced and this group differences was found to be significant with z value 4.762 and p value <0.0001

Limitations

- The retrospective nature of the analysis
- Small number of enrolled patients
- Effect of other drug on D-dimer level not analyzed
- Study results are preliminary and hypothesis generating; Larger multicentre prospective studies are required to confirm our preliminary finding

Conclusion

- This retrospective observational study shows that treatment with enoxaparin during hospital stay was associated with decrease in D –dimer level in patients admitted to hospital for COVID-19.
- Since the usefulness of enoxaparin in improving clinical outcome in COVID-19 patients seems consistent and its use is routine in many covid hospitals, there is urgent need of multicentric trials to evaluate its clinical efficacy in COVID-19 patients

Conflict of interest- None

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