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A Pharmacoeconomics Study for Anticoagulants used for Hospitalized COVID-19 Patients in Al-Najaf Al-Ashraf city –Iraq(Conference Paper)#

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Abstract

Hematologic complications are one of the major consequences in patients with COVID-19 infection. Anticoagulants were used to mitigate COVID-19 related coagulopathy such as Enoxaparin and unfractionated Heparin.To investigate the differences between Enoxaparin and unfractionated Heparin using a cost-effectiveness analysis that compares the clinical outcome and the costs of two anticoagulants. . A retrospective review of medical records of hospitalized, severe to critical COVID-19 infected patients was conducted at Al-Amal hospital at Al-Najaf city-Iraq from August 2020 to June 2021. D-dimer level, length of stay (LOS), and survival rate were used to assess the effectiveness, and the cost of both medications was also evaluated for comparison. . One hundred and forty-four COVID-19 infected patients were enrolled and divided into Heparin group N=72, and Enoxaparin group N=72. COVID-19 infected patients had a higher level of D-dimer than the reference range (2534.675 ng/dl). No significant differences in average D-dimer between both genders. There was a significant difference between patients' ages ≥60 years and patients <60. Higher D-dimer levels were associated with a higher mortality rate. Heparin was more effective in decreasing D-dimer levels than Enoxaparin which inversely increased the D-dimer levels. Additionally, Heparin was associated with higher survival rate compared to Enoxaparin. It was associated with a longer duration of stay in hospital than Enoxaparin however, no significant difference was observed. Heparin cost/per patient/per day was less than Enoxaparin. . Heparin was a more cost-effective anticoagulant therapy compared to Enoxaparin, it was associated with a lower cost and better effect.

Keywords: Pharmacoeconomic cost-effectiveness, COVID-19, Anticoagulants, Heparin, Enoxaparin.

دراسة الاقتصاديات الدوائية لمضادات التخثرالمستخدمة لمرضى كوفيد-١٩ الراقدين في مدينة النجف الاشرف/العراق (بحث مؤتمر)#

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 # المؤتمر العلمي التاسع لكلية الصيدلة ، جامعة بغداد ٢٥ – ٢٦ اب ٢٠٢١
*فرع الصيدلة السريرية، كلية الصيدلة، جامعة بغداد، بغداد/العراق

الخلاصة

المضاعفات المرتبطة بالدم هي احد التبعات الرئيسية للمرضى المصابين بفايروس كوفيد-١٩، حيث يتم استخدام مضادات التخثر للتخفيف من التخثر، كالاينوكزابارين والهيبارين لز اكتشاف الفرق بين من مضادات التخثر (الهيبارين و الاينوكزابارين) باستخدام تحليل الفعالية الاقتصادية الذي يقارن النتائج والكلفة لاثنان من مضادات التخثر. الدراسة كانت مراجعة باثر رجعي لسجلات المرضى المصابين اصابة شديدة الى حرجة بفايروس كورونا والراقدين في مستشفى الامل في محافظة النجف في العراق، من آب ٢٠٢٠ الى يونيو ٢٠٢١، حيث تم استخدام معدل دي دايمر، مدة الرقود في المشفى، ومعدل النجاة لقياس الفعالية الدوائية و تم احتساب كلفة الدواء فقط في التحليل. تم تضمين ١٤٤ مريض في الدراسة مقسمة الى ٧٢ مريض تلقوا علاج الهيبارين و ٧٢ مريض تلقوا علاج الاينوكزابارين. وقد اظهرت النتائج بأن المرضى المصابين بفايروس كورونا كان لديهم معدل دي دايمر من الحد الطبيعي المحدد في المصادر(٢٥٣٤,٦ نغ/دل). ولم يكن هناك فرق ملحوظ بين الجنسين في المعدل الاساسي للدي دايمر .كان هنالك فرق ملحوظ في المعدل الاساسي للدي دايمر بين الاعمار اكبر ويساوي ٦٠ عاما واصغر من ٦٠ عاما . كما يبدو ان المعدلات الاعلى للدي دايمر كانت مرتبطة بشكل ملحوظ بمعدل وفيات اعلى. الهيبارين كان اكثر فعالية من الاينوكزابارين في تقليل مستويات الدي دايمر. بالاضافة الى ذلك فان الهيبارين كان يرتبط بمعدل نجاة اعلى بالمقارنة مع الاينوكزابارين . كما انه كان يرتبط بمدة بقاء اطول في المستشفى بالمقارنة مع الاينوكزابارين لكن الفرق كان غير ملحوظا. بما يخص الكلفة فان كلفة الهيبارين كانت اقل من كلفة الايناكزابارين / للمريض الواحد/ ليوم واحد). الهيبارين كان ذو فعالية اقتصادية اعلى بالمقارنة مع الاينوكزابارين، حيث انه يرتبط بكلفة اقل وفعالية افضل.

الكلمات المفتاحية: الاقتصاديات الدوائية، الفعالية الاقتصادية، كوفيد-١٩، مضادات التخثر، هيبارين، اينوكزابارين.

Introduction

Coronavirus is a newly discovered virus[(1)], it is deemed a pandemic by WHO in January/2020 [(2)], where the first case of COVID-19 was reported in December 2019 in Wuhan, China, from that date, 180 million cases were reported globally until June 25.2021, with 3.9 million deaths. In Iraq, 1.3 million cases were reported, with 17,000 deaths [(3)]. Symptoms of COVID-19 Infection cause respiratory syndrome, which overlaps with other viral syndromes. It includes fever, headache, fatigue, shortness of breath, diarrhea, cough, and myalgias[(4)]. Furthermore, abnormalities could be seen in chest x-ray and computed tomography (CT)[(5)].

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Laboratory findings include leukopenia and lymphopenia [6], elevated levels of aminotransferase, C-reactive protein (CRP), D-dimer, S.ferritin, and lactate dehydrogenase (LDH). It also leads to cardiac[7], hematologic[8], renal[9], and other complications.

Thromboembolic events occur in patients with COVID-19, with the highest risk occurring in critically ill patients[10] where the incidence of thromboembolism among hospitalized patients with COVID-19 ranged from 25 to 53% [11]. It has been found that infection with COVID-19 is related to an increase in Padua prediction score >4 in 40% of patients, (padua score was developed to estimate risk of venous thromboembolism (VTE) in hospitalized medical patients [12] where a score >4 indicates a higher risk of venous thromboembolism [13]. COVID-19 infection potentiates all 3 components of Virchow's triad (endothelial dysfunction, hypercoagulable state, and stasis). It increases the risk of thrombosis, endothelial dysfunction which is triggered by angiotensin-converting enzyme 2 (ACE2), and result in an increase in D-dimer, fibrin/fibrinogen. In addition, thrombin time is affected and becomes shorter[14,15]while prothrombin time, and activated partial thromboplastin time appears to be longer [16].

Currently, the world health organization (WHO)[17], recommend prophylaxis dose of anticoagulants, low molecular weight Heparin (Enoxaparin) 40 mg by subcutaneous injection every 24h: - If BMI > 40 kg/m2 or weight > 120 kg: Enoxaparin 40 mg by subcutaneous injection every 12h. Or Unfractionated Heparin (UFH) 5000 units by subcutaneous injection every 8 or 12h: - If BMI > 40 kg/m2 or weight > 120 kg: 7500 units q12h or 5000 units every 8h.

Enoxaparin and unfractionated Heparin are both on the WHO Model List of Essential Medicines; Enoxaparin has the advantage of daily dosing and the suggested duration of standard thromboprophylaxis is until hospital discharge. If therapeutic dosing is prescribed, clinicians should be aware of the increased risk of bleeding, including major bleeding requiring transfusion (e.g. gastrointestinal) or clinically significant bleeding even if transfusion is not required (e.g. intracranial). Factors influencing the choice of agent include: the availability of laboratory monitoring (needed for unfractionated Heparin); requirement for rapid reversibility (favors unfractionated Heparin); presence of severe renal dysfunction (favors unfractionated Heparin); interaction with other drugs used to treat COVID-19 (especially direct oral anticoagulants);, convenience (least with unfractionated Heparin, most with direct oral anticoagulants); and suspicion of Heparin-induced thrombocytopenia (favors fondaparinux or direct oral anticoagulants).

For therapeutic or intermediate intensity anticoagulation, patients should have baseline creatinine, platelet count, prothrombin time or international normalized ratio, and partial thromboplastin time. Patients on therapeutic dosing of unfractionated Heparin require monitoring of partial thromboplastin time or anti-factor Xa levels and ideally platelet count (18).

As the treatments of COVID 19 infection continues to evolve, the health service provider needs to understand the effect of potential treatments on the primary outcomes (e.g. mortality, mechanical ventilation, duration of hospital stay); understand their effects with regards to different parameters such as; age, respiratory support requirement, disease severity, and race/ethnicity together with the immensity of clinical benefit, as this will be necessary to make the best decision. (19). Of note, the COVID-19 pandemic did not affect the health only but its effects have been extended to the social and economic aspect therefore, many studies focused on estimating the cost of COVID-19 disease and its treatments to understand the impact on economic aspects (20,21). Other researches were studied the clinical effects of COVID-19 treatments, however, there is a paucity in studies conducted to understand and explain both cost and effectiveness of COVID-19 treatments. (see discussion section).

Objective

The study aimed to conduct a cost-effectiveness analysis comparing the clinical outcome and the costs of two anticoagulant injections (unfractionated Heparin and low molecular weight Heparin (Enoxaparin)) used to treat hospitalized, severe-critical COVID-19 infected patients.

Methodology

Study design and patients

The study was a retrospective review of medical records for hospitalized patients diagnosed with severe - critical COVID-19 infection.

Inclusion criteria

Hospitalized patients with COVID-19 infection, age > 18 years, non-pregnant, and received one of the injectable anticoagulants, for 3 days and more, with at least two measurements for the D-dimer (the first one before receiving

the treatments and the second one at the last day of receiving the treatments. Patients who were not fit these criteria were excluded from the study.

Sample size

Searching in patient's medical records continue until the two arms became equal, Heparin arm N=72, Enoxaparin arm N=72, with allocation ratio 1:1, 1100 patient's records were reviewed until equality had been achieved. The equation for finite population (22) was used to estimate the sample size where the confidence level is 95%, the estimated sample size is 139, which means the strength of the sample size is more than 100%, also the equality of the two arms gives the sample size a statistical strength.

Study setting and ethical approval

The study was conducted at Al-Amal hospital, at Al-Najaf city from (Augast 2020 to June 2021) after obtaining the approval from the scientific committee of the University of Baghdad/ College of Pharmacy and the Iraqi Ministry of Health/ Al-Najaf Department of Health/ Department of Research and Development.

Data sourcing

All medical data were taken from patient's medical records, and the cost of treatments was taken from the drugs store which supplied Al-Amal hospital.

Cost-effectiveness analysis of two injectable anticoagulants (unfractionated Heparin and low molecular weight Heparin (Enoxaparin)) was conducted.

Outcome measures

The clinical outcomes of original injectable anticoagulants (low molecular weight Heparin (Enoxaparin) and unfractionated Heparin) were assessed using D-dimer levels, duration of hospitalization, and survival rate. Where D-dimer level aids in the diagnosis of venous thromboembolism (VTE) [23,24].

In the beginning, some demographic assessments were done to know if the baseline readings of D-dimer were affected by gender and age to avoid bias. Gender distribution was demonstrated as male and female, the age distribution was categorized into groups (<60 years and ≥ 60 years). There was no distribution according to race or ethnicity in this study.

Then analysis was conducted to ensure the normality of distribution of the sample, the age and comorbidities of the two arms were compared. Then the average baseline of D-dimer in patients with COVID-19 infection was assessed to understand the effect of COVID-19 on D-dimer levels.

The effects of original injectable anticoagulants (Heparin and Enoxaparin) on D-dimer level, length of stay, and survival rate were then assessed.

average of differences between 1st and 2nd reading of D-dimer /per day/per patient was considered as a primary clinical outcome of anticoagulants therapies). It was calculated by dividing the difference between the 1st and 2nd D-dimer reading of the patient by the number of days the patient received the treatment, then the summation of the differences per day divided by the number of patients who received the treatment.

Secondary outcomes: length of stay was calculated as an average for each treatment group.

The survival rates during hospitalization days of the patients were calculated using Kaplan-Meier to show the survival rate over time of hospitalization. Also, it was calculated in the descriptive method, where it is equal to number of patients who survived at the end of hospitalization time divided by the total number of patients who received the treatment. Both the Kaplan-Meier method and the descriptive method gave the same survival rate.

Economic outcome

A- The costs of medications were taken from the drugs store which supplied Al-Amal hospital during the same period of data collection, so there was no need to count the inflation rate or the discount factor.

B- The cost of hospitalization: the average cost of one day of hospitalization was 53.6 $US, which includes the cost of health service providers, cost of medical instruments, cost of medication, and non-medical costs. This cost was taken from the Iraqi Ministry of Health/Department of Financial Planning in 2017. The inflation factors in Iraq were then multiplied with the average cost for the period from 2017 to 2021[25].

C- Willingness to pay: The average maximum willingness to pay of Iraqi people was obtained from the responses of 375 people who were participated in a web-based survey, hypothetical scenarios were used to ask people about the maximum amount they are willing to pay for special benefits using multiple-choice questions. The survey was conducted by the author at the same period of conducting the study. So there was no need for inflation rate or the discount factor, and there was no need for sensitivity analysis because there were 375 responses.

Cost-effectiveness analysis

Cost vs effect was represented by: cost consequence analysis method, cost-effectiveness ratio CER method while incremental cost-effectiveness ratio was conducted when needed.

To conduct a cost-effectiveness analysis, two methods were used: 1st by using the cost-effectiveness plane, and the 2nd method is called incremental net benefit analysis (INB) which considers maximum willingness to pay as an effector on cost-effectiveness analysis.

Statistical analysis

All data were collected, assembled, analyzed using a Microsoft Excel spreadsheet, The effect of the treatments on the indicator was calculated as an average change in number per patient per day and compared using independent student T.test.

Additional statistical analysis to assess the impact of treatments upon the survival outcome variable. Kaplan-Meier survival curves were plotted to measure the survival rates using Statistical Package for the Social Sciences software (SPSS) Version 24.

The normality of continuous variables was measured using the Shapiro-Wilk test. Not normally distributed variables were tested using non-parametric tests.

Results

D-dimer value had been used to evaluate the effectiveness of anticoagulants (Heparin and Enoxaparin). Before conducting the comparison, the D-dimer baseline average was calculated for COVID-19 infected patients before receiving any treatment. See (Table 1) .

Table 1. D-dimer baseline average for hospitalized, COVID-19 infected patients before receiving any treatment.

Indicator	Average	Normal average	P-value	N
D-dimer baseline average for hospitalized patients with COVID-19 infection	2534.675 ng/dl ± SD=2923	<500 ng/dl	$0.0005 * 10^{-3}$	144

One sample student t.test, P-value < 0.05 is significant.

The effect of demographic characteristics on D-dimer level

The average baseline D-dimer value was calculated regarding the demographic variations to understand if the D-dimer was influenced by gender and age, and to understand if the baseline measurement had an effect on the final status of the patients, died or survived.

D-dimer baseline average before receiving the treatment was higher in males than females, but the difference was non-significant (P-value >0.05).

D-dimer baseline average was higher in patients age ≥60 years than patients age <60 years. The difference in average according to age was significant. (P-value <0.05).

Higher D-dimer levels seem to be associated with a higher mortality rate, the D-dimer baseline average was significantly higher in patients who died than patients who survived (P-value <0.05). See (Table 1-2)(Figure1-1).

Table 2. D-dimer baseline average according to gender (male, female), age, and final status.

Demography	Average D-dimer ng/dl	SDV ng/dl	Percentage%	N	p. value
Total	2534.675	± 2923	100	144	
Heparin group	3349.8	±3081.5	50		0.00005
Enoxaparin group	1637.76	±1634.03	50		
Gender					
Male	2649.95	± 3365.729	58.2	84	0.7
Female	2374.10	± 2213.854	41.8	60	
Age (Years)					
≥60 Years	3177.33	± 3514.531	54.4	78	0.04
<60 Years	1763.06	± 1699.574	45.6	66	
Final status					
Died`	3166.263	± 3422.71	55.9	80	0.04
Survived	1729.94	± 1829.12	44.1	64	

This table measured the difference in means of D-dimer (continous variable) according to binary (categorized variable) using independent T-test. , P-value < 0.05 is significant.

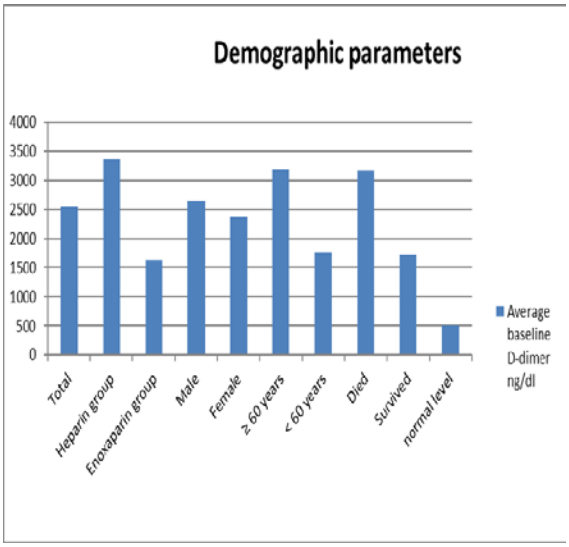

Figure 1. D-dimer baseline average according to gender (male, female), age, and final status.

Comparison of age and comorbidities of Heparin and Enoxaparin groups

A comparison was performed between the age and comorbidities of the group who received unfractionated Heparin, and the group who received low molecular weight Heparin (Enoxaparin). The analysis showed that there were no significant differences with regard to the age and comorbidities of both groups of treatment. (P-value >0.05). See (Table 1-3).

Table 3. Average age of hospitalized patients who received Anticoagulants (Heparin and Enoxaparin), and the type and percentage of comorbidities for each group.

Indicator	Heparin	Enoxaparin	P-value
Average age (years)	61.9 ±15.9	58.5 ± 12.9	**0.159**
Type and percentage of comorbidities (co-existed diseases)			**0.86**
Hypertension	73.6	70.8	0.84
Diabetes mellitus	47.2	45.8	0.9
Ischemic heart disease	29.2	18	0.17
Asthma	6.9	4.2	0.47
Renal disease	2.77	0	0.16
Liver disease	0	4.2	0.08
Type and percentage of comorbidities from patients vital signs			**0.87**
Severe infection	68.05	68.05	1
Critical infection	31.9	31.9	1
O2 supplementation	100	100	1
S. creatinine ≥1.5 mg/dl	12.5	0	0.0027
S. urea > 20 mg/dl	100	100	1
S. urea>100 mg/dl	8.3	12.5	0.43
ESR > 40 mm/hr	68.05	65.3	0.74
Blood pressure >130/80 mm Hg	19.4	20.8	0.85
Blood pressure < 90/60 mm Hg	2.77	5.55	0.41
Heart rate >100 Bpm	26.38	22.22	0.61
Heart rate <60 Bpm	5.55	2.77	0.41
Low grade fever 37.5-38.5 C̊	18	5.55	0.029
High grade fever >38.5 C	0	0	1

Independent student t.test used to compare all comorbidities of the two groups **(bold)**, Chi-square test used to compare each comorbidity (categorical) with the other group, P-value < 0.05 is significant

Clinical outcome

The primary outcome for assessing the effectiveness of Heparin and Enoxaparin was the effect of those two medications on reducing D-dimer levels, Heparin was significantly more effective on reducing D-dimer levels than Enoxaparin, Enoxaparin had a negative outcome in reducing D-dimer levels (P-value <0.05). See (Table 1-4) and (Figure 1-2).

Table 4. The effect of anticoagulant therapies on the level of D-dimer of hospitalized patients with COVID-19.

Indicator	Heparin	Enoxaparin	P-value
Average of 1st D-dimer reading nd/dl	3349.806	1637.769	0.00005
Average of 2nd D-dimer reading ng/dl	3012.108	2479.214	0.29
Difference between average D-dimer before treatment and after treatment (delta)	Decreased 337.698	Increased 841.445	0.01
Average difference of D-dimer per day per patient	Decreased 24.4/ng/dl/day ± 226.614	Increased 154.701ng/dl/day ± 504.6	0.01

Independent student t.test, P-value < 0.05 is significant .

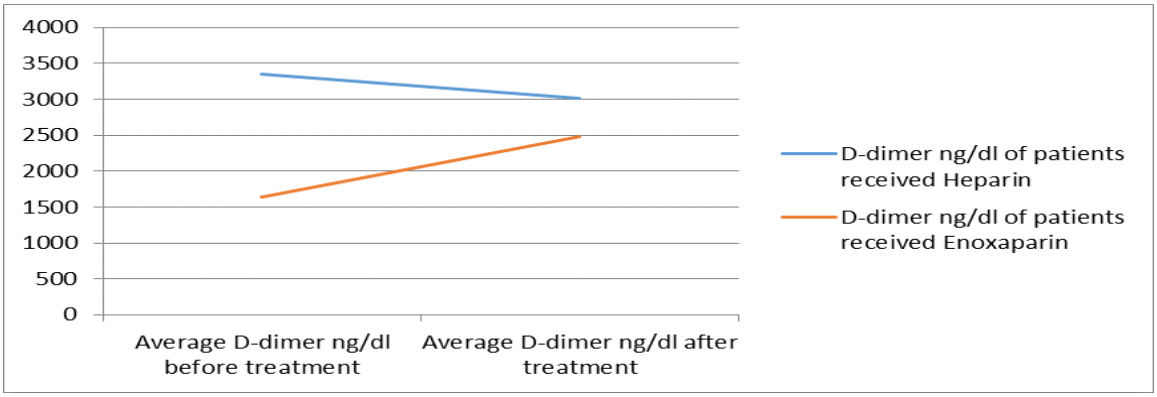

Figure 2. The effect of anticoagulant therapies on the level of D-dimer of hospitalized, severe –critical **COVID-19 infected patients.**

The secondary outcome for assessing the effectiveness of anticoagulants (Heparin and Enoxaparin) was an average length of stay (LOS) in hospital, the group who received Enoxaparin had a shorter average for length of stay (LOS) than the group who was treated with Heparin, but the difference on (LOS) was non-significant (P-value >0.05). See (Table 1-5) and (Figure 1-3).

Table 5. Average length of stay in hospital (days) for patients with COVID-19 infection who received Anticoagulants therapies (Heparin and Enoxaparin).

Indicator	Heparin	Enoxaparin	P-value
Average length of stay (days)	13.7 ± 8.1	12.3 ± 9.9	0.37

Independent student t.test, P-value < 0.05 is significant.

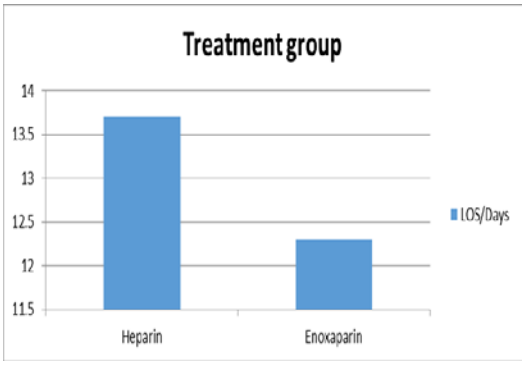

Figure 3. Average length of stay in hospital (days) for patients with severe-critical COVID-19 infection who received Anticoagulants therapies (Heparin and Enoxaparin).

The last outcome used to assess the effectiveness of Heparin and Enoxaparin was the survival rate during hospitalization time, it is calculated by dividing the number of patients who survived at the end of the period of treatment by the number of total patients who received the treatment n=72 then multiplied by 100%.

The group of patients who were treated with Heparin showed a higher survival rate (lower mortality rate) during hospitalization days than the group of patients who were treated with Enoxaparin during hospitalization days, the difference between the survival rate of the two groups was significant (P-value<0.05). See (Table 1-6), (Table 1-7) and (Figure 1-4).

Table 6. Survival rate and test of equality of survival distributions for hospitalized patients with COVID-19 infection who received injectable anticoagulants (Heparin, Enoxaparin)

Indicator	Heparin	Enoxaparin	
Survival rate	55%	35%	
Test	**Chi-Square**	**F**	**Sig.**

Log Rank (Mantel-Cox)	5.332	1	.021

Chi-square test, P-value < 0.05 is significant.

Table7.Case Processing Summary, 1=Heparin, 2=Enoxaparin, event =survival.

Treatment	Total N	N of Events	Censored	
			N	Percent
1	72	32	40	55.6%
2	72	47	25	34.7%
Overall	144	79	65	45.1%

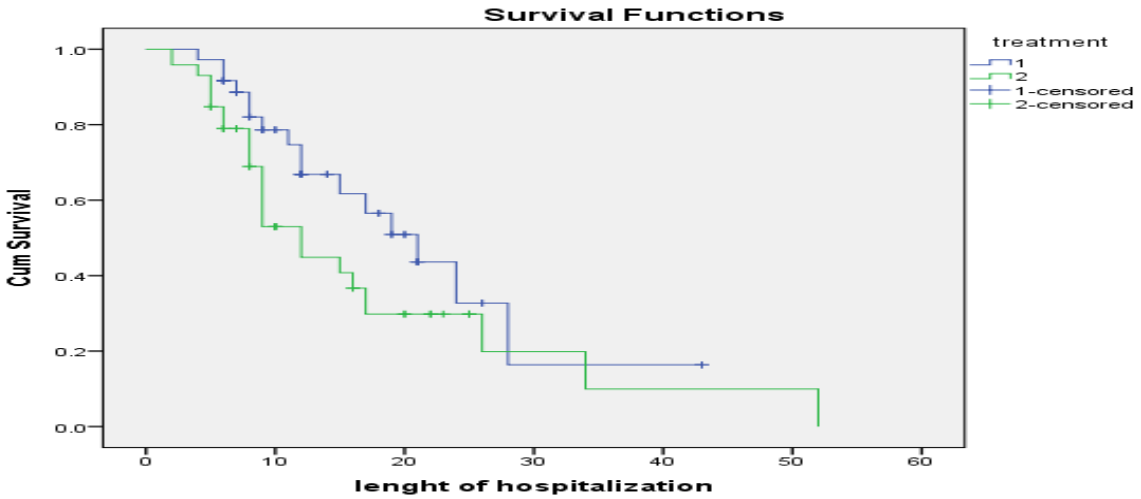

Figure 4. Kaplan Meier survival curve during hospitalization (days) for original Heparin=1, and original Enoxaparin =2, for hospitalized, severe –critical COVID-19 infected patients. Status 1= survival, test = Log Rank (Mantel-Cox).

Costs of anticoagulants

Costs of anticoagulants converted from Iraqi dinars into U.S dollars, and then the average cost of treatments only was calculated for the patient per one day. The total cost of Heparin for 72 patients who were treated with doses of 986 days was calculated, and the cost of Enoxaparin for 72 patients who were treated with doses of 889 days was also calculated.

The cost of hospitalization was calculated by multiplying the average cost of one day of hospitalization by the average duration of hospitalization. (Table 8)

Table 8. Costs of treatment with anticoagulants (Heparin and Enoxaparin) of hospitalized, severe –critical COVID-19 infected patients.

Treatment/cost	Heparin	Enoxaparin
Cost US$/dosage form	2.28 /5ml	2.95/4000unit
Average cost US$ /day/patient	2.08±0.5 /day/patient	9.44±1.9/day /patient
Total cost for 72 patients in US$ during hospitalization days.	1,885.7/986 days/72 patients	8,279.91/889 days/72 patients
The average cost (US$) of hospitalization for each patient	809.122	726.44

Presentation of cost vs effectiveness

Table 9. presentation of cost vs effectiveness of anticoagulants (Heparin and Enoxaparin) for hospitalized, severe –critical COVID-19 infected patients.

1. Cost consequence analysis		
Treatment	**Heparin**	**Enoxaparin**
Total cost in $ US for 72 patients	1,885.7/986 days/72 ptients	8,279.91/889 days/72 patients
Average cost in $ US per day per patient	2.08 ± 0.5$/day/patient	9.44 ± 1.9$ /day/patient
Outcome		
Average D-dimer difference per day	Decreased -24.4 ± 26.614ng/dl/day	Increased +154.70 ± 504.6 ng/dl/day
Survival rate	55%	35%
The average length of stay (days)	13.7 ± 8.1	12.3 ± 9.9
2. Average cost-effectiveness ratio (CER):		
Average cost in $ US per unit (1ng/dl) of D-dimer changed per day per patient	2.08/24.4= 0.085 $ U.S per 1 ng/dl of D-dimer decreased	9.44/-154.7= 0.061 $ U.S per 1 ng/dl of D-dimer increased
Cost in $ U.S per one percent increase in survival rate	1,885.7 $/55= 34.28$ per one percent of survival rate	8,279.91$ /35= 236.56 $ per one percent of survival rate
The average cost in $ U.S of decreasing hospitalization duration for one day.	809.122 $/13.7day= 59.06 $ per day	726.44$/12.3 day= 59.06 $ per day
3. Incremental cost-effectiveness ratio: Heparin compared to Enoxaparin		
Outcome	**Incremental cost-effectiveness ratio (ICER)**	
The average change in D-dimer level per day	(2.08-9.44)/(-24.4(ng/dl)-154.7(ng/dl))= 0.041$ saved per extra unit of D-dimer decreased.	
Survival rate	(1,885.7 $- 8,279.91 $)/55%-35%= 319.71$ saved per one percent increase in survival rate.	

Cost-effectiveness analysis

Cost-effectiveness plane

Heparin had a lower cost and higher effect compared to Enoxaparin so it is located at the negative side of y-axes= -7.36, and the positive side of x-axes= +179.1, at quadrant (II) which means Heparin is cost-effective (Dominant). See (Figure 5)

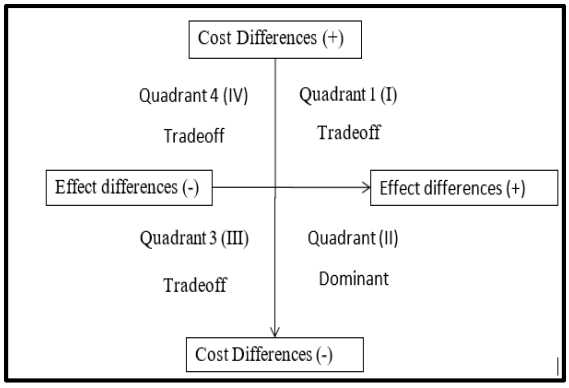

Figure 5 .Cost –effectiveness plane ,graphical presentation of cost – effectiveness of anticoagulants used for hospitalized severecritical COVID-19 infected patients.

Incremental net benefit analysis

INB= (Lambda * (effect of Heparin – effect of Enoxaparin)) –(cost of Heparin – cost of Enoxaparin)

Equation 1. incremental net benefit equation.

Average willingness to pay to decrease the level of D-dimer from the abnormal average of COVID-19 infected patients to the normal range was= 45.9$.

The D-dimer level should be reduced by 2034.67 ng/dl to be within the normal range. So WTP to reduce one unit of D-dimer was = 45.9$/2034.67 ng/dl= 0.022$ / 1 ng/dl of D-dimer

INB = (0.022$ * (24.4-(-154.701))-(2.08-9.44)= +11.3

The positive result means that Heparin is more cost effective than Enoxaparin.

Discussion

The current study has shown that levels of D-dimer of COVID-19 infected patients were higher than normal range (p.value <0.05). There are many reasons which might contribute to this rise in D-dimer values in COVID-19 patients such as: I) infection which can cause the release of pro-inflammatory cytokines, thus causing an inflammatory storm[26]. II) Some patients with COVID-19 have different degrees of hypoxia and inflammation which could lead to thrombosis or increased oxygen consumption[27]. III)Severe infection or acute inflammation caused by sepsis could also affect blood coagulation[28] therefore, D-dimer tests are extremely useful for the diagnosis of thrombotic diseases hence, patients with COVID-19 were reported to have a hypercoagulable state[29].

D-dimer levels are associated with the severity of COVID-19 infection, where higher D-dimer levels were associated with a high mortality rate. Number of studies have shown that the severity of patients with COVID-19 was significantly related to D-dimer concentrations. Meanwhile, the severe COVID-19 patients tend to have a higher concentration of D-dimer when compared with non-severe patients. This suggests that D-dimer could be used to evaluate the severity of infection[30-31]

The D-dimer levels in patients who died from the infection were significantly higher than those of surviving cases [32] where 71% of patients who died from COVID-19 were found to have met the disseminated intravascular coagulation (DIC) standard**[16]**.

Critical D-dimer values are associated with advanced age, male gender, dyspnea, hypertension, coronary heart disease, diabetes, and cerebrovascular disease ($p < 0.05$). **[33]**.

Results of this study found that there is no effect of gender on D-dimer levels while, abnormal D-dimer values were identified in patients over 60 years old age ($p < 0.001$). Other studies suggest that higher D-dimer levels are associated with the male gender**[33]**, and others showed it is associated with the female gender where women were at a higher risk of developing thrombotic disorders in COVID-19 infection[34]. Overall, it seems that, there is an association between age and D-dimer levels **[33,34]**.

Of note, the results of the present study have shown that treatment with Heparin was more effective in decreasing D-dimer levels and mortality rates than Enoxaparin, but it was associated with a longer duration of stay. These results are in contrast with other studies which found that Enoxaparin was more effective than Heparin as anticoagulant therapy for COVID-19 infected patients. Patients who administered Enoxaparin had a lower mortality rate, lower ICU admission rates, and shorter hospital / ICU stays than those who received unfractionated Heparin[35].

Previous studies have suggested that Enoxaparin may be more effective than unfractionated Heparin in certain cases of treatment and prophylaxis of coagulopathies., for example in the prevention of venous thromboembolism (VTE)[36,37]. Furthermore, some studies reported that Enoxaparin treatment in COVID-19 might be effective not only as anticoagulants but also has an anti-inflammatory effect. Therefore, starting Enoxaparin treatment in the earlier stage will decrease the risk of micro-thrombosis in vital organs[38].

This controversy in results leaves several questions and possibilities. It might be due to the different effects of anticoagulants in different D-dimer values. Patients with D-dimer levels < 1 µg/mL did not appear to benefit from anticoagulation while patients with D-dimer levels > 10 µg/mL derived the most benefit[39]. In addition, different FDA indications were reported for Enoxaparin[40] and Heparin[41]. The label of Enoxaparin includes the prophylaxis and treatment of deep vein thrombosis (DVT) with or without pulmonary embolism (PE) in various settings, while the label of Heparin includes similar prophylactic indications as well as the treatment of a broader spectrum of acute embolic events including peripheral arterial embolism and embolism in the setting of atrial fibrillation.

It is worth mentioning that, the results of this study may be influenced by unmeasured variables which are not recorded in this dataset, such as; prothrombin time (PT), partial thromboplastin time (PTT), the international normalized ratio (INR), erythrocyte sedimentation rate (ESR), respiratory rate (RR), inflammatory cytokines (cytokine storm).

Other contributory factors which might have a role in the findings are: the circumstances of storage of the biological anticoagulants; the correct doses and methods of administrations for anticoagulants; different circumstances of carrying out D-dimer tests because the proficiency of testing are highly variable from one mthod to another. Notebly, changing the type or magnitude of units from that recommended by the manufacturer are associated with as much as a 20-fold increase in the failure of proficiency testing of D-dimer. **[24]**

With regards to the cost, Heparin has a lower cost than Enoxaparin, (this includes only the cost of medication), taking into account the difficulties in estimating other costs such as indirect costs, non-medical costs, and additional costs that result from side effects of the treatment.

On the other hand, other studies revealed that Enoxaparin is associated with a significant cost-saving impact when used for therapy for patients with venous thromboembolism compared to IV Heparin [42,43]. In contrast, other studies reported that Enoxaparin is associated with a non-significant reduction in total hospital costs compared with the appropriate use of UFH prophylaxis[44].Overall, the results of the present study motivate further studies to investigate reasons for differences in the outcomes and future trials that could enable the development of a more efficacious standard of practice in regards to the administration of anticoagulants in COVID-19 patients. Prospective analysis comparing the efficacy of Enoxaparin and unfractionated Heparin is warranted [35].

Conclusion

Originator Heparin was a more cost-effective anticoagulant therapy compared to originator Enoxaparin, it had a better effect in decreasing D-dimer level and higher survival rate, where the differences in the effect on those two outcomes were significant. In addition, Heparin was associated with a lower cost, treatment with Heparin has resulted in positive INB= 11.3, where a positive result means that Heparin is more cost-effective than Enoxaparin. The two methods of pharmacoeconomic analysis have revealed that Heparin was more cost-effective than Enoxaparin in treating COVID-19 infected patients.

References

1. Coronavirus [Internet]. WHO.int. 2021 Available from: https:// www. who.int/health-topics /coronavirus#tab=tab_1
2. Timeline: WHO's COVID-19 response [Internet]. WHO.int. 2021 Available from: https:// www. who. int/ emergencies /diseases/ novel-coronavirus-2019/interactive-timeline#!
3. Johns Hopkins. COVID-19 dashboard by the Center for Science and Engineering. 2021. Available at https:// coronavirus .jhu. edu/ map.html. Accessed june 25, 2021.
4. Xie J, Tong Z, Guan X, Du B, Qiu H. Clinical Characteristics of Patients Who Died of Coronavirus Disease 2019 in China. JAMA Network Open. 2020;3(4):e205619..
5. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases. 2020;20(4):425-434.
6. Zhou P, Yang X, Wang X, Hu B, Zhang L, Zhang Wm et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.
7. Liu P, Blet A, Smyth D, Li H. The Science Underlying COVID-19. Circulation. 2020;142(1):68-78.
8. Henry B, de Oliveira M, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM). 2020;58(7):1021-1028.
9. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. Journal of the American Society of Nephrology. 2020;31(6):1157-1165.
10. Bikdeli B, Madhavan M, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up. Journal of the American College of Cardiology. 2020;75(23):2950-2973.
11. Maldonado E, Tao D, Mackey K. Antithrombotic Therapies in COVID-19 Disease: a Systematic Review. Journal of General Internal Medicine. 2020;35(9):2698-2706.
12. Padua Prediction Score for Risk of VTE [Internet]. Reference.medscape.com. 2021 [cited 10 October 2021]. Available from: https://reference.medscape.com/calculator/388/padua-prediction-score-for-risk-of-vte
13. Wang T, Chen R, Liu C, Liang W, Guan W, Tang R et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. The Lancet Haematology. 2020;7(5):e362-e363.
14. Talasaz A, Sadeghipour P, Kakavand H, Aghakouchakzadeh M, Kordzadeh-Kermani E, Van Tassell B et al. Recent Randomized Trials of Antithrombotic Therapy for Patients With COVID-19. Journal of the American College of Cardiology. 2021;77(15):1903-1921.
15. Han H, Yang L, Liu R, Liu F, Wu K, Li J et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clinical Chemistry and Laboratory Medicine (CCLM). 2020;58(7):1116-1120.
16. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020;18(4):844-847.
17. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. WHO/2019-nCoV/clinical/2020.4. World Health Organization;2020.
18. COVID-19 Clinical management: living guidance [Internet]. Who.int. 2021 [cited 21 September 2021]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1.
19. Sheinson D, Dang J, Shah A, Meng Y, Elsea D, Kowal S. A Cost-Effectiveness Framework for

COVID-19 Treatments for Hospitalized Patients in the United States. Advances in Therapy. 2021;38(4):1811-1831.

20. Alhusseiny A, Latif I, Ali Jadoo S. COVID-19 in Iraq: an estimated cost to treat patients at a private clinics. Journal of Ideas in Health. 2021;4(1):304-306.

21. Beck da Silva Etges A, Bertoglio Cardoso R, Marcolino M, Brasil Ruschel K, Coutinho A, Pereira E et al. The Economic Impact of COVID-19 Treatment at a Hospital-level: Investment and Financial Registers of Brazilian Hospitals. Journal of Health Economics and Outcomes Research. 2021;8(1):36-41.

22. calculator s. Sample Size Calculator [Internet]. Calculator.net. 2021. Available from: https:// www. Calculator .net/sample-size-calculato.html? type=1 & cl =95& ci=5 &pp=10 &ps=2000000 &x= 67 &y=28.

23. Moresco R, Vargas L, Voegeli C, Santos R. D-dimer and its relationship to fibrinogen/fibrin degradation products (FDPs) in disorders associated with activation of coagulation or fibrinolytic systems. Journal of Clinical Laboratory Analysis. 2003;17(3):77-79.

24. Olson J, Cunningham M, Higgins R, Eby C, Brandt J. D-dimer: Simple Test, Tough Problems. Archives of Pathology & Laboratory Medicine. 2013;137(8):1030-1038.

25. Iraq - Inflation rate 2026 | Statista [Internet]. Statista. 2021. Available from: https:// www. statista. com/statistics/327290/inflation-rate-in-iraq/

26. Chousterman B, Swirski F, Weber G. Cytokine storm and sepsis disease pathogenesis. Seminars in Immunopathology. 2017;39(5):517-528.

27. Gupta N, Zhao Y, Evans C. The stimulation of thrombosis by hypoxia. Thrombosis Research. 2019;181:77-83.

28. Iba T, Levy J, Warkentin T, Thachil J, Poll T, Levi M. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. Journal of Thrombosis and Haemostasis. 2019;17(11):1989-1994.

29. Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E et al. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. Thrombosis and Haemostasis. 2020;120(06):998-1000.

30. Du W, Zhang Y, Yu Y, Zhang R. D-dimer levels is associated with severe COVID-19 infections: A meta-analysis. International Journal of Clinical Practice. 2021.

31. Zhan H, Chen H, Liu C, Cheng L, Yan S, Li H et al. Diagnostic Value of D-Dimer in COVID-19: A Meta-Analysis and Meta-Regression. Clinical and Applied Thrombosis/Hemostasis. 2021;27:107602962110109.

32. Long H, Nie L, Xiang X, Li H, Zhang X, Fu X et al. D-Dimer and Prothrombin Time Are the Significant Indicators of Severe COVID-19 and Poor Prognosis. BioMed Research International. 2020;2020:1-10.

33. He X, Yao F, Chen J, Wang Y, Fang X, Lin X et al. The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. Scientific Reports. 2021;11(1).

34. Sharp K, Ghodke B. D-dimer Levels in COVID-19 Patients and Its Correlation with Age and Gender: A Retrospective Analysis. International Journal of Research and Review. 2020;7(7):339-347.

35. Pawlowski C, Venkatakrishnan A, Kirkup C, Berner G, Puranik A, O'Horo J et al. Enoxaparin is associated with lower rates of mortality than unfractionated Heparin in hospitalized COVID-19 patients. EClinicalMedicine. 2021 ;33 :100774.

36. Laporte S., Liotier J., Bertoletti L. Individual patient data meta-analysis of Enoxaparin vs. unfractionated Heparin for venous thromboembolism prevention in medical patients. J Thromb Haemost. 2011;9:464–472.

37. McGarry L, Thompson D, Goldhaber S, Stokes M, Weinstein M. PCV14 cost-effectiveness of thromboprophylaxis in acutely-ill medical inpatients. Value in Health. 2002;5(3):166-167.

38. Ugur M, Adiyeke E, Recep E, Bakan N, Yiyit N. Aggressive thromboprophylaxis improves clinical process and decreases the need of Intensive Care Unit in Covid-19. Pakistan Journal of Medical Sciences. 2021;37(3).

39. Billett H, Reyes-Gil M, Szymanski J, Ikemura K, Stahl L, Lo Y et al. Anticoagulation in COVID-19: Effect of Enoxaparin, Heparin, and Apixaban on Mortality. Thrombosis and Haemostasis. 2020;120(12):1691-1699.

40. United States Food and Drug Administration. Lovenox (Enoxaparin sodium injection) for subcutaneous and intravenous use.

41. United States Food and Drug Administration. heparin sodium, for intravenous use.Menon H, Pillai A, Aussenberg-Rodriguez J, Ambrose J, Youssef I, Griffiths E et al. Cost reduction associated with Heparin-induced thrombocytopenia panel ordering for Enoxaparin versus Heparin for prophylactic and therapeutic use: A retrospective analysis in a community hospital setting. Avicenna Journal of Medicine. 2018;8(04):133-138.

42. Weinberg, Richard & Lichtig, Leo & Caprini, Joseph & Merli, Geno & Vogenberg, F Randy & Rph, Cost Implications of Using Unfractionated Heparin or Enoxaparin in Medical Patients at Risk for Venous Thromboembolic Events. (2006).P and T. 31,

43. Amin A, Lin J, Lenhart G, Schulman K. Economic Outcomes in Patients at Risk for Venous Thromboembolism Receiving Appropriate Enoxaparin or Unfractionated Heparin Prophylaxis. Blood. 2008; 112 (11) :1285 -1285