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CLINICAL STUDY

Comparison of standard prophylactic and preemptive therapeutic low molecular weight heparin treatments in hospitalized patients with COVID-19

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ABSTRACT

INTRODUCTION: Anticoagulant treatment approach in patients with COVID-19 is not well studied and not standardized. We aimed to compare the effects of standard prophylactic and pre-emptive therapeutic Low-Molecular-weight Heparin (LMWH) treatment approaches on mortality in patients with COVID-19.

PATIENTS AND METHODS: This retrospective and single-centre study includes patients aged ≥ 18 years, who were diagnosed with COVID-19 and treated with LMWH during the hospital stay. Therapeutic dose of LMWH was defined as 1 mg/kg subcutaneously twice daily and prophylactic dose of LMWH was defined as 40 mg subcutaneously once daily.

RESULTS: Among the 336 patients diagnosed with COVID-19 pneumonia, 115 patients, who received LMWH were included in the study. The mean age was 58.6 ± 13.3 and 58 (50.4 %) of the patients were male. Sixty-nine (60 %) of the patients were treated with prophylactic and 46 (40 %) therapeutic LMWH. In-hospital mortality was not different between patients treated therapeutic LMWH and prophylactic LMWH by the multivariate regression analysis (OR=2.187, 95% CI 0.484–9.880, p=0.309) and the propensity score modelling (OR=1.586, 95% CI 0.400–6.289, p=0.512.)

CONCLUSION: Clinicians should consider the potential risks and benefits of standard prophylactic and pre-emptive therapeutic LMWH. Therefore, anticoagulant therapy should be individualized in patients with COVID-19 *(Tab. 3, Ref. 28)*. Text in PDF *www.elis.sk*

KEY WORDS: anticoagulant therapy, COVID-19, Low-molecular-weight heparin (LMWH), mortality, outcome.

Introduction

The disease caused by a newly discovered beta coronavirus, SARS-CoV-2, has been named the Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) (1). After the first COVID-19 case reported in Wuhan, China in December 2019, the disease spread rapidly and was declared as a pandemic by the WHO (2). COVID-19 has caused mortality and morbidity, especially multiple complications. Coagulopathy is one of the serious complications of COVID-19. Autopsy results demonstrated deep vein thrombosis, pulmonary microthrombi and embolisms in patients with COVID-19 (3). As seen in Coronavirus infections, the systemic inflammatory response seen in severe COVID-19 patients may result in coagulation disorders. Any imbalances between procoagulant, anticoagulant, and fibrinolytic homeostatic mechanisms may cause hypercoagulability or bleeding (4, 5). Moreover, studies suggested that anticoagulants reduce mortality in the patients with severe disease (6, 7). Despite the lack of information about coagulopathy mechanism, coagulation disorders in COVID-19 are certain and therefore, anticoagulant treatment is mostly commenced prophylactically and therapeutically in COVID-19 patients. However, anticoagulant treatment approach in the patients with COVID-19 is not well studied and not standardized (8, 9, 10). Therefore, in this study, we aimed to compare the effects of standard prophylactic and preemptive therapeutic Low Molecular Weight Heparin (LMWH) treatment approaches on mortality in the patients with COVID-19.

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Patients and methods

Study design and patients

This retrospective and single-centre study includes patients aged ≥ 18 years, who were diagnosed with COVID-19 and treated at least three days with LMWH during the hospital stay between March 11 and April 11, 2020. Exclusion criteria were as follows: 1) patients with negative results of SARS-CoV-2 by reverse-transcriptase real-time polymerase chain reaction. 2) patients, who were not treated with LMWH during their inpatient stay; 3) patients receiving other forms of anticoagulant; 4) patients, who received therapeutic LMWH for a thrombotic indication.

Therapeutic dose of LMWH was defined as 1 mg/kg subcutaneously twice daily and prophylactic dose of LMWH was defined as 40 mg subcutaneously once daily. Prophylactic and therapeutic LMWH were administered by the trained physicians based on the disease severity and d-dimer levels. However, there was no definite protocol for the anticoagulant treatment regimen. As increased D-dimer levels were mostly found in patients with thrombotic complications, patients with increased D-dimer levels were prophylactically or therapeutically treated with LMWH to reduce thrombotic events and mortality (6–12). Mortality was defined as all-cause in-hospital death.

Data collection

The demographic data, age, gender, underlying diseases, symptoms, physical examination findings, laboratory parameters and radiological results, the treatments and outcomes were recorded via a follow-up datasheet. We recorded body temperature, respiratory rate, heart rate, arterial blood pressure, oxygen saturations at the time of first presentation to hospital and calculated the National Early Warning Score 2 (NEWS2) score to identify the severity of the disease. Laboratory results and radiological examinations were included if performed within 24 hours of admission and after LMWH treatment.

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences, IBM SPSS, version 21 (SPSS Inc, Chicago, USA). Demographic and clinical features were described by mean ± standard deviation, median (minimum–maximum) for continuous variables, and frequency (n) and percentages (%) for categorical variables. Chi-Square test and Fisher's exact test were used to compare the differences in proportions of categorical variables between the groups. Kolmogorov–Smirnov test was used for normal distribution. Independent Samples t-test and Mann-Whitney U-test were used for comparison of continuous variables between the two independent groups. The value of $p < 0.05$ was accepted to be statistically significant. To compare the mortality between the two groups of LMWH dosage, univariate and multivariate analyses were performed. Additionally, logistic regression analysis with a propensity score adjustment was performed to mitigate biases attributable to covariate imbalances in the group characteristics.

Tab. 1. The demographic and clinical characteristics of COVID-19 patients.

	In Total		Prophylactic LMWH		Therapeutic LMWH		*p*
	n	%	n	%	n	%	
Number of patients	115	100	69	60	46	40	
Age							
Mean ± sd	56.8±13.3		56.9±14.5		56.8±11.4		0.975[c]
Median	58(20–80)		57(20–80)		59.5(27–79)		
Gender							**0.010** [a]
Male	58	50.4	28	40.6	30	65.2	
Female	57	49.6	41	59.4	16	34.8	
Underlying diseases	77	67.0	45	65.2	32	69.6	0.627[a]
COPD	3	2.6	1	1.4	2	4.3	0.563[b]
Diabetes mellitus	38	33.0	21	30.4	17	37.0	0.466[a]
Hypertension	44	38.3	29	42.0	15	32.6	0.309[a]
Sign and symptoms							
Fever	52	45.2	30	43.5	22	47.8	0.646[a]
Cough	84	73.0	51	73.9	33	71.7	0.797[a]
Dyspnea	51	44.3	31	44.9	20	43.5	0.878[a]
Myalgia	13	11.3	7	10.1	6	13.0	0.631[a]
Arthralgia	4	3.5	3	4.3	1	2.2	0.649[b]
Body temperature							0.078[d]
mean	36.9±0.7		36.8±0.60		37.02±0.74		
median (min–max)	36.7 (36–39.1)		36.7 (36.0–38.7)		37(36.0–39.1)		
Respiratory rate/ minute							**0.010** [d]
mean	22.7±5.1		21.5±3.3		24.5±6.6		
median (min–max)	22(15–40)		20(16–35)		22(15–40)		
Heart rate/minute							0.137[d]
mean	89.1±13.8		87.7±13.5		91.5±14.2		
median (min–max)	88(57–138)		86(57–138)		89(64–120)		
SpO2							0.393[d]
mean	91.2±6.3		92.2±4.4		89.8±8.3		
median (min–max)	93 (65–99)		93(76–99)		92(65–99)		
NEWS2<7	62	53.9	55	79.7	7	15.2	**<0.001**[a]
NEWS2≥7	53	46.1	14	20.3	39	84.8	

COPD = Chronic obstructive pulmonary disease, SpO2 = peripheral capillary oxygen saturation, min= minimum; max = maximum, NEWS2 = The National Early Warning Score 2, [a] Chi-Square Test, [b] Fisher's Exact Test, [c] Independent. Samples T Test, [d] Mann–Whitney U Test.

Results

General characteristics

Among the 336 patients diagnosed with COVID-19 pneumonia, 115 patients, who received LMWH were included in the study. Sixty-nine (60 %) of the patients were treated with prophylactic and 46 (40 %) with therapeutic LMWH. The mean age was 58.6 ± 13.3 and 58 (50.4 %) of the patients were male. Among patients, who received therapeutic LMWH, male gender was more common ($p = 0.010$). There was no significant difference in both groups in terms of age and underlying diseases. There were also no significant differences in COVID-19 pneumonia onset symptoms, with the inclusion of fever (temperature ≥ 37.4 °C), cough, dyspnoea, myalgia, and arthralgia (Tab. 1). However, only respiratory rate was higher in the therapeutic group ($p = 0.010$). C-reactive protein and D-dimer levels were significantly higher in the patients receiving therapeutic doses of LMWH (respectively; $p = 0.012$, $p < 0.015$). There was no significant difference in the conventional therapies between the groups (Tab. 2).

Risk of mortality

The length of hospital stay (13.4 ± 6.1 days vs 10.9 ± 6.8 days, $p = 0.004$), the need for mechanical ventilation (50.0 % vs 14.5 %, $p < 0.001$), the admission to inten-

Tab. 2. Laboratory parameters, Treatments and Clinical outcomes of COVID-19 patients.

	In total		Prophylactic LMWH		Therapeutic LMWH		p
	mean	sd	mean	sd	mean	sd	
Laboratory parameters							
Leukocyte (/μL)	6218	2384	6375	2442	5984	2301	0.352 [d]
Neutrophile (/μL)	4408	2056	4477	2061	4304	2066	0.723 [d]
Lymphocyte (/μL)	1256	563.0	1334	647.3	1140	382.9	0.208 [d]
Platelet (x103)	192.9	72.3	196.9	70.3	187.0	75.7	0.269 [d]
CK (IU/L)	236.6	370.6	225.1	406.4	253.3	315.4	**0.024** [d]
Albumin (g/L)	34.5	5.0	35.8	4.2	32.7	5.4	**0.004** [c]
Ferritin (ng/mL)	291.7	244.2	265.1	211.5	338.1	290.2	0.295 [d]
CRP (mg/L)	79.2	67.0	64.1	50.6	101.7	81.4	**0.012** [d]
Procalcitonin (μg/L)	0.3	0.5	0.1	0.2	0.5	0.8	**<0.001** [d]
D-dimer (μg/L)	1.3	3.0	0.8	0.4	2.2	4.8	**0.015** [d]
Treatments							
Hydroxychloroquine	106	92.2	63	91.3	43	93.5	0.671 [a]
Oseltamivir	96	83.5	56	81.2	40	87.0	0.412 [a]
Azithromycin or Clarithromycin	112	97.4	68	98.6	44	95.7	0.563 [b]
Ceftriaxone	98	85.2	56	81.2	42	91.3	0.133 [a]
Lopinavir/Ritonavir	32	27.8	16	23.2	16	34.8	0.174 [a]
Favipravir	30	26.1	14	20.3	16	34.8	0.083 [a]
Tosilizumab	5	4.3	2	2.9	3	6.5	0.388 [b]
Corticosteroid	25	21.7	11	15.9	14	30.4	0.065 [a]
Clinical outcomes							
Non-invasive ventilation	35	30.4	11	15.9	24	52.2	<0.001 [a]
Invasive ventilation	33	28.7	10	14.5	23	50.0	<0.001 [a]
ICU	36	31.3	13	18.8	23	50.0	<0.001 [a]
Death	25	21.7	5	7.2	20	43.5	<0.001 [a]
LOS in hospital (mean ± std)	11.9±6.6		10.9±6.8		13.4±6.1		0.004 [d]

CRP=C-reactive protein; ICU=Intensive care unite; LOS=Length of stay; sd=standard deviation; a=Chi-Square Test; b=Fisher's Exact Test; c=Independent Samplest Test; d=Mann-Whitney U Test

Tab. 3. Univariate and multivariate analyses for mortality in patients with COVID-19.

	Univariate Analysis			Multivariate Analysis		
	OR	(95% CI)	p value	OR	(95% CI)	p value
Male Gender	2.54	0.995–6.483	0.051	1.457	0.421–5.042	0.552
Age	1.025	0.989–1.062	0.183	1.050	0.992–1.111	0.092
C-reactive protein	1.016	1.008–1.025	**<0.001**	1.014	1.004–1.023	**0.005**
Therapeutic LMWH	9.846	3.341–29.017	**<0.001**	2.187	0.484–9.880	0.309
NEWS ≥ 7	53.143	6.844–412.6	**<0.001**	21.486	2.213–208.647	**0.008**

LMWH = Low Molecular Weight Heparin, NEWS2 = The National Early Warning Score 2

sive care unit (ICU) (50.0 % vs 18.8 %, p = 0.001) and mortality (43.5 % vs 7.2 %, p < 0.001) were significantly higher in the therapeutic group treated with LMWH compared to those treated with prophylactic LMWH (Tab. 2). Male gender, dyspnoea, low oxygen saturation, high body temperature, increased respiratory rate, receiving lopinavir/ritonavir, favipravir, corticosteroid therapy, high level of C-reactive protein, procalcitonin, urea, low level of albumin, longer duration of hospital stay, the need for ICU and mechanical ventilation, and receiving prophylactic LMWH were associated with mortality (p < 0.05). In univariate analysis, in-hospital mortality was higher in the therapeutic LMWH group (OR = 9.846, 95% CI 3.341–29.017, p < 0.001). Mortality was not different between therapeutic and prophylactic LMWH groups when we adjusted gender, age, C-reactive protein and NEWS2 (OR = 2.187, 95% CI 0.484–9.880, p = 0.309) (Tab. 3). This difference remained after adjusting for gender, CRP, D-dimer, and NEWS2 by propensity score (OR = 1.586, 95% CI 0.400–6.289, p = 0.512).

Discussion

In our study, mortality (43.5 % vs 7.2 %, p < 0.001) was significantly higher in the therapeutic group treated with LMWH compared to those treated with prophylactic LMWH. However, mortality was not different between patients treated with therapeutic LMWH and prophylactic LMWH by the multivariate regression analysis (OR = 2.187, 95% CI 0.484–9.880, p = 0.309) and the propensity score modelling (OR = 1.586, 95% CI 0.400–6.289, p = 0.512).

There is an increasing number of studies indicating that LMWH is effective in reducing mortality in patients with COVID-19 (6, 7). However, only a few studies compared therapeutic and prophylactic doses of LMWH treatments (13–19). Whereas some studies showed advantages (7, 11) and disadvantages (12–16) of therapeutic LMWH, others found no difference on clinical outcomes/mortality (17–19). Paranjpe et al reported that patients, who received anticoagulants were more likely to need an invasive mechanical ventilation (29.8 % vs 8.1 %, p < 0.001), and among the mechanically ventilated patients, the mortality rate was lower in the patients, who were treated with anticoagulant than those, who were not treated with anticoagulant (29.1 % vs 62.7 %) (7). Additionally, Paoliss et al reported that receiving therapeutic LMWH therapy was associated with a lower in-hospital mortality compared to the prophylactic LMWH (13). In contrast, in the study of Motta et al, the mortality was 2.3 times higher in patients, who received therapeutic dose LMWH than those, who received prophylactic dose LMWH (14). Musoke et al emphasized the higher mortality and increased bleeding complications in those receiving therapeutic dose anticoagulant therapy (15). In the study of Hsu et al, 30-day mortality rate was statistically higher in the patients receiving therapeutic anticoagulation (40 %), when compared to the standard (15 %) and high-intensity prophylaxis cohorts (6 %) (16). The randomized clinical trial (17) showed that therapeutic LMWH improved gas exchange and decreased the ratio of unsuccessful weaning from the ventilator. In the same study, although the mortality rate was not significantly different, it was found to be higher in those receiving therapeutic LMWH than those receiving prophylactic LMWH, what is consistent with our study. Nadkarni et al. showed that when compared toh prophylactic anticoagulant, therapeutic anticoagulant was associated with a lower mortality,

although not statistically significant (18). Also, Klok et al found that there was no difference in mortality in the patients receiving therapeutic anticoagulation, although they found an increase in thromboembolic events (19). Additionally, anticoagulation treatment has limited (20) or not significant (21) effect on thrombosis in the patients with COVID-19.

Thromboembolic events and cytokine storm release caused by the development of coagulopathy have significant impact on COVID-19 prognosis (22, 23). The dysfunction of endothelial cells induced by infection, resulting in an excessive thrombin production and inhibition of fibrinolysis, indicates hypercoagulability in the patients with COVID-19. In the pathogenesis of severe acute respiratory syndrome associated with Coronavirus, high plasma inflammatory cytokines (interleukin 1, 6, 8, and 12), tumour necrosis factor, interferons, and chemokines takes place in the severe storm (24, 25). Some studies showed that anticoagulant treatment had positive effects on clinical outcomes and laboratory parameters in the patients with COVID-19 (6, 7, 13, 26, 27). Tang et al. suggested that COVID-19 severity was associated with D-dimer and Fibrin degradation products (28). Also, they found that LMWH was associated with a better prognosis in severe COVID-19 patients with elevated D-dimer levels or meeting Sepsis-Induced Coagulopathy criteria (6). LMWH is known to have not only anticoagulant, but also anti-inflammatory effects. Shi et al showed that LMWH reduced percentage of lymphocytes d-dimer and IL-6 levels in patients with COVID-19 (26). Also, Yormaz et al showed that the count of lymphocytes ($OR = 0.356$, $p < 0.001$), D-dimer ($OR = 0.974$, $p < 0.001$) and CRP levels ($OR = 0.628$, $p < 0.001$) were significantly improved in the LMWH group, as compared to the control group (27).

This study has several strengths. Firstly, multiple comorbidities and different types of variables such as: vital signs, laboratory parameters and radiological findings were included in the multivariate regression analysis. Secondly, we excluded patients with laboratory un-confirmed COVID-19. Our study had also several limitations. Firstly, it was retrospectively conducted in a single-centre. Secondly, this study had a small sample size and a control group was not included. The generalizability of our results may be limited. Third, physicians might tend to recommend therapeutic treatment for severe cases during the first month of the pandemic. However, we used propensity score modelling to make the outcomes comparable in the two cohorts, by adjusting for covariates, because LMWH treatment was not randomly assigned.

Conclusion

In conclusion, we did not find an association between therapeutic LMWH and mortality in hospitalized patients with COVID-19 even after adjusting for covariates. Clinicians should consider the potential risks and benefits of standard prophylactic and preemptive therapeutic LMWH. Therefore, anticoagulant therapy should be individualized in patients with COVID-19. However, we need new large-scale studies and randomized controlled trials providing important information to better understand anticoagulant therapy in the patients with COVID-19.

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