Original Research Article

Effect of anticoagulants on the survival rate in critically ill COVID-19 patients

ABSTRACT

Background: The World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19), as a pandemic in January 2020. The morbidity and mortality associated with the disease are enormous COVID-19, with a multi-systemic pathology, exhibits thrombosis as a common manifestation. Disseminated intravascular coagulation (DIC) and thrombotic lesions have been reported in >70% and >30% of patients, respectively, who have died due to the COVID-19 and therefore, heparin is included in the treatment of moderate to severe cases. This retrospective study was undertaken to check the effectiveness of prophylactic therapy with heparin at reducing mortality in critically ill COVID-19 patients.

Methodology: The study included retrospective data from case records of 169 critically ill COVID-19 patients with or without comorbidities and an anticoagulant regimen. The data were thoroughly studied for demographic profile, comorbidities, type and dosage of anticoagulants, length of intensive care unit stay, and mortality rates.

Results: The male to female ratio of the study subjects was 125/44 (76%/24%). Patients with comorbidities were critically ill as compared to those with none (140/29), and diabetes mellitus was the most common comorbidity, found in 99 patients. Mortality rate was significantly higher in patients who had not received any anticoagulant ($p = 0.015$) and in patients who had received unfractionated heparin ($p = 0.036$) as compared to those who received low molecular weight heparin (LMWH).

Conclusion: The prophylactic administration of heparin improves the survival rate of the critically ill covid 19 patients is more when compared with the patients who do not receive heparin. LMWH is very effective in reducing thrombotic complications and mortality in critically ill COVID-19 patients.

Key words: thrombosis, low molecular weight heparin, COVID-19, coagulopathy

INTRODUCTION

The World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19), as a pandemic in January 2020. The morbidity and mortality associated with the disease are enormous, with a profound, global, and devastating impact on every aspect of human life, with healthcare facilities and workers being affected the most.

The presentation of COVID-19 patients varies from being asymptomatic to succumbing to sudden death. Almost all the organs in the body are affected to varying magnitudes, with respiratory compromise being the most common manifestation of this disease. The basic pathogenesis behind multisystemic involvement rests on the occurrence of coagulation disorders. High levels of circulating D-dimer levels are associated with higher mortality rates [1,2]. Autopsy of COVID-19 patients has confirmed the presence of fibrin thrombi within small vessels and capillaries with large amount of extracellular fibrin deposition [3]. Coagulopathy observed in COVID-19 patients shows an inconsistent pattern, varying from bleeding diathesis to thrombotic consequences. Disseminated intravascular coagulation (DIC) and thrombotic lesions have been reported in >70% and >30% of patients, respectively, who have died due to the COVID-19 [4]. Abnormal laboratory tests of coagulation also seem to vary with the severity of illness and the clinical predictors of risk of bleeding or thrombosis [5]. A prolonged prothrombin time (PT) and an elevated D-dimer have been shown to increase mortality and thereby heighten the need for critical care [4,6]. Radiological diagnosis of thromboembolism (TE) using computed tomography and ultrasonography has been very challenging in this pandemic era due to the lack of infrastructure to deal with this massive surge of infective patients and other logistic issues. High incidence of TE has paved the way for empiric escalation of anticoagulants by some investigators; however, consensus has not been reached on whether prophylactic or escalated dose is required to prevent these thrombotic events [7]. Various doses of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) have been recommended for anticoagulation therapy in COVID-19 patients [8].

This retrospective study was undertaken to analyze the importance of empirical use of anticoagulants in the survival rate of critically ill COVID-19 patients in a tertiary healthcare center.

METHODOLOGY

The study was approved by the institutional ethics committee. A total of 169 adult patients of age >18 years, with a positive COVID-19 report and admitted in the Intensive Care Unit (ICU) of our hospital, between May 2020 to November 2020, were included in the study.

Data were obtained retrospectively by a manual review of the patient case records from the department of medical record maintenance of the hospital. Patient data collected were the demographic details; relevant comorbidities, if present, like preexisting diabetes mellitus, hypertension, ischemic heart disease, chronic lung disease, and chronic kidney disease; anticoagulants administered, if any, along with the type, dose, and frequency as decided by the healthcare center depending upon the status of renal function and D-dimer values; length of ICU stay; and mortality. The outcome of the patients in the form of survival or mortality was compared among the ones who received no anticoagulants with the ones who received anticoagulants once

or twice daily with the help of Chi square test. Furthermore, survival outcomes were compared among the patients who received LMWH 40 mg OD and BD, 60 mg OD and BD, and UFH, with the help of Fisher exact

test.

The demographic details of the 169 COVID-19 patients included in the study are summarized in Table 1, and the incidence of various comorbidities recorded in the patients are summarized in Table 2. Of the 169 patients, comorbidities were present in 140 patients, with diabetes mellitus being the most common (58.6%) of all the comorbidities evident. Of the 169 patients included in the study, 14 patients did not receive any anticoagulant, and 131 and 24 patients received anticoagulant dose once and twice daily, respectively, and there was a significant difference in the survival rates among all the groups of patients. The best survival outcome was seen in patients who received once daily dose of anticoagulants (Table 3).

When the survival rates were compared among the patients receiving 40 mg or 60 mg LMWH, once or twice daily, no significant difference was found in the survival rates, thus, the survival not being significantly affected by the dose or frequency of LMWH. However, there was a significant difference in the improvement of survival yielded by LMWH and UFH, with better chances of survival being offered by LMWH (Table 4).

Conclusively, it was found that the patients who received anti-coagulants showed 3.28 times better survival as compared to those who did not receive anticoagulants (Table 5).

Table 1: Demographic details of the COVID-19 patients

Variable	Category	Mean ± SD / n (%)
Age	--	58.25 ± 15.56
Gender	Male	125 (74%)
	Female	44 (26%)
Comorbidities	Yes	140 (82.8%)
	No	29 (17.2%)
Average ICU stay (in days)	--	7.17 ± 3.88

Table 2: Comorbidities in the COVID-19 patients

Variable	Category	N (%)
Diabetes mellitus	Yes	99 (58.6%)
	No	70 (41.4%)
Hypertension	Yes	85 (50.3%)
	No	84 (49.7%)
Ischemic heart disease	Yes	32 (18.9%)
	No	137 (81.1%)
Chronic lung disease	Yes	10 (5.9%)
	No	159 (94.1%)
Chronic kidney disease	Yes	16 (9.5%)
	No	153 (90.5%)

Table 3: Effect of anticoagulant administration in the patients

Anticoagulants	N	Survived N (%)	Dead N (%)	χ^2 value	P value
No anticoagulant	14	4 (4.3%)	10 (13%)	8.371	0.015*
Once daily anticoagulation dose	131	79 (85.9%)	52 (67.5%)		
Twice daily anticoagulation dose	24	9 (9.8%)	15 (19.5%)		
Total	**169**	**92 (100%)**	**77 (100%)**		

chi-square test; * indicates significant difference at $p \leq 0.05$

Table 4: Comparison of the survival and mortality rates using different dosage of LMWX and unfractionated heparin

Heparin	Mortality			χ^2 value	p value
	Survived	Dead	Total		
LMWX 40 OD	16 (69.6%)	7 (30.4%)	23 (100%)	0.264	0.800 (NS)
LMWX 40 BD	42 (63.6%)	24 (36.4%)	66 (100%)		
LMWX 60 OD	3 (60%)	2 (40%)	5 (100%)	0.012	1.000 (NS)
LMWX 60 BD	8 (57.1%)	6 (42.9%)	14 (100%)		
LMWX	69 (63.9%)	39 (36.1%)	108 (100%)	4.825	0.036*
UFH	9 (39.1%)	14 (60.9%)	23 (100%)		

Fisher exact test; NS: non-significant; *indicates significant difference at $p \leq 0.05$

Table 5: Association of mortality status with administration of anticoagulants

Factors	OR	95% Confidence Interval	
		Lower	Upper
Anti-coagulants/ No anti-coagulants	3.284	0.987	10.927

DISCUSSION

The pathophysiology of COVID-19 infection on human organ system is still not fully understood due to its varied clinical presentation and severity. However, numerous studies have confirmed an underlying coagulopathy as the main causative factor for the several systemic manifestations and multiorgan dysfunction syndrome, with a resultant hypercoagulable state, resulting in micro and macro circulatory thrombotic events like pulmonary embolism, deep vein thrombosis, arterial thrombosis, and DIC. Additionally, Tang et al observed DIC as a cause of mortality in 71.4% of the patients [4]. Elevated D-dimer level is a strong and independent risk factor for mortality in the COVID-19 patient [1]. Thrombosis occurs most frequently in the lungs, despite a systemic immunoinflammatory response, hence, often called as “pulmonary intravascular coagulopathy.” As pathological confirmation of such condition is not possible in a living person, the presence of high levels of D-dimer helps by indicating the presence of microthrombosis in vast areas of the lungs [9]. As a prognostic indicator, it is recommended that all patients with confirmed COVID-19 should undergo serial coagulation analysis, particularly D-dimer levels, prothrombin time, and platelet count [10].

Severe form of COVID-19 with coagulopathy is associated with higher mortality when compared to survivors [11]. Daughety et al observed 27.6% higher mortality in patients with TE, possibly due to the endothelial injury and hypercoagulability induced by the generalized inflammation. According to the authors, in patients with severe disease, escalated dose thromboprophylaxis, i.e., with 0.5 mg/kg of enoxaparin twice daily or heparin infusion titrated to anti factor Xa levels of 0.3–0.5 U/ml, was found to reduce the rate of inpatient venous TE in renal failure patients [12]. Likewise, Barnes et al recommended 40 mg or 0.5 mg/kg subcutaneous twice-daily dose of enoxaparin or 7,500 U subcutaneous thrice-daily dose of UFH [13].

In our study, although different dose and frequency of L MWH had no significant difference in survival advantage offered, there was a significant difference in the outcome with the use of LMWH and UFH, with LMWH showing better survival outcome than the UFH. Thachil et al, witnessing a decreased mortality rate with the use of anticoagulants in all patients and specifically in patients with sepsis-induced coagulopathy score of >3, strongly suggested the use of prophylactic dose of anticoagulants, preferably of LMWH, unless contraindicated, such as in acute kidney injury where UFH can be used [14]. Likewise, as per the guidelines and expert panel report issued by Moores et al, LMWH or fundoparinox is recommended as against UFH for

all critically ill COVID-19 patients, the advantage being lower risk of heparin-induced thrombocytopenia and decreased risk of exposure to the nursing staff in view of single dose delivery [15]. In Japan, a combination

of UFH (LMWH being approved by the insurance system only for proven DIC and hemodialysis) and nafamostat (a serine protease inhibitor) is used and has shown promising results.[9]

The effect of systemic anticoagulants to prevent the pathological changes is unclear. The postulated theory for the benefit of heparin usage includes the anti-inflammatory properties of heparin, which can block thrombin formation, and the anti-viral property, which inhibits viral attachment by binding on SARS-CoV-2 surface receptor binding protein [16]. A case series demonstrating beneficial use of tissue plasminogen activator in refractory hypoxia has also been reported [17]. Our study clinically supports the effectiveness of anticoagulants in improving the survival of critically ill COVID-19 patients, with 3.28 times better survival seen in patients under anticoagulants as against those who did not receive any anticoagulant.

In our study, although there was a lack of freedom to choose the dose and drug for thromboprophylaxis due to the retrospective study design, based on available literature and initial experience of COVID-19 patients, the chosen regimens were accepted with rational justifications and the patients were included in the study.

Despite prophylactic initiation of anticoagulants, radiological evidence of venous TE was observed by Lax et al in 60% of ICU patients when compared to 10% of ward patients, and autopsy revealed microscopic thrombi in the small–middle sized arteries of the lungs in all the 11 cases in their study [18]. Carsana et al observed pulmonary microthrombi and alveolar hemorrhage in autopsied lungs of patients with anticoagulant therapy, coincidentally both occurring with a frequency of 87%.[19]

Limitations of the study

1. Coagulopathies, as diagnosed clinically or by laboratory parameters, were not included in the study.
2. Correlation between anticoagulants, comorbidities, and mortality was not attempted.
3. Morbidity or complications due to various types and dosage of heparin was not included.

CONCLUSION

This retrospective analysis of critically ill COVID-19 patients suggests that prophylactic administration of heparin improves survival rate when compared to patients who do not receive heparin. Furthermore, LMWH was found to be a better alternative to UFH in terms of reduced mortality rate.

REFERENCES

1. Zhou F, YuT, Du R. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet.2020;395 (10229):1054-1062. 2)
2. Guan WJ, Ni ZY, Hu Y, China Medical Treatment Expert Group for COVID-19 clinical Characteristics of Coronavirus Disease 2019 in China. N Eng J Med. 2020;382(18):1708-1720
3. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19 : an autopsy series from New Orleans. Lancet Respir Med 2020 Jul; 8(7):681-686.
4. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.
5. Samkari HA, Karp LRS, DziK WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020 Jul 23; 136(4): 489-500.
6. Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
7. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: implications for prevention, antithrombotic therapy and follow-up. J Am Coll Cardiol 2020 Jun 16; 75(23): 2950-2953.
8. Obi AT, Barnes GD, Wakefield TW, et al. Practical diagnosis and treatment of suspected venous thromboembolism during COVID-19 pandemic. J Vasc Venous Lymphat Disod.2020 Jul; 8(4):526-5349)
9. Asakura H, Ogawa H. COVID-19 associated coagulopathy and disseminated intravascular coagulation. Int Jof Hematol 113,45-57 (2021)
10. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost.2020. doi :10.1111/jth.14817
11. Agnes Y, Lee Y. Connors JM, Kreuziger LB, Murphy M, Gernsheimer T, Lin Y, Huisman M, DeSancho M. COVID-19 and Coagulopathy: Frequently Asked Questions. American Society of Hematology, COVID-19 Resources. COVID-19 and Coagulopathy. Version 7.0; last updated Jan 29, 2021.

12. Daughety MM, Morgan A, Frost E, Kao C, Hwang J, Tobin R, Patel B, Fuller M, Welsby I, Ortel T. COVID-19 associated coagulopathy: Thrombosis, hemorrhage and mortality rates with an escalated–dose thromboprophylaxis strategy. Thromb Res 2020 Dec;196: 483-485.
13. Barnes GD, Burnett A, Allen A, Blumenstein M, Clark NP,cuker A, Dager WE, Deitelzweig SB, Garcia D, Kaatz S, Minichiello T. Thromboembolism and anticoafgulant therapy during the COVID-19 Panademic: interim clinical guidance from the anticoagulation forum. Journal of Thrombosis and Thrombolysis. 2020 50:72-81
14. Thachil J, Tang N, Gando S, et al ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost.2020. doi:10.1111/jth.14810
15. Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, Holley AB, Jumenez D, Le gal G, Rali P, Wells P. Prevention, Diagnosis and Treatment of VTE with Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. CHEST 2020;158(3): 1143-1163
16. Mycroft-West CJ, Su D, Elli S, et al. The 2019 coronavirus (SARS-CoV-2) surface protein (Spike) S1 Receptor Binding Domain undergoes conformational change upon heparin binding. bioRxiv. 2020:2020.02.29.971093/ doi:10.1101/2020.02.29.971093
17. Wang J, Hajizedah N, Moore EE, et al. Tisssue Plasminogen Activator (tPA) Treatment for COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): A Case Series. J Thromb Haemost.2020.doi:10.1111/jth.14828
18. Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, et al. Pulmonary arterial Thrombosis in COVID-19 With Fatal Outcome: Results From a Prospective, Single-center Clinicopathologic case series. Ann Intern Med. 2020;173(5):350-061.
19. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study, Lancet Infect Dis. 2020. Oct;20(10): 1135-1140.