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ORIGINAL ARTICLE

Effect of Anticoagulant Administration in patients Hospitalized with COVID-19 - A study from Lahore, Pakistan

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ABSTRACT

Background: The recognition of the relationship between thromboembolism in COVID-19 and poor clinical outcomes led to the use of anticoagulants in patients diagnosed with COVID-19.
Aim: To determine the effects of anticoagulants in COVID-19 patients and to compare the effect of oral, subcutaneous, and combined anticoagulants on patient outcomes.
Study design: Retrospective cohort study
Place and duration: A private tertiary care hospital, in Lahore, from 1st April 2020 to 30 Sep 2020
Methodology: Data were collected from electronic and paper records of admitted patients with a confirmed diagnosis of COVID-19 on PCR or with a radiological diagnosis of COVID-19**.** A total of 179 patients were included in the study, 172 were given anticoagulation, out of these, 74 were given oral anticoagulation, 73 were given subcutaneous and 24 were given combination of oral and subcutaneous anticoagulants.
Results: Among 172 patients on anticoagulants, 41(23.8%) expired while 131(76.2%) recovered. Among 7(100%) patients on no anticoagulation, 1(14.3%) patient expired while 6(85.7%) recovered. 19(11%) patients on anticoagulation progressed towards the need for invasive ventilation while 152(89%) patients did not need invasive ventilation. Among patients on subcutaneous anticoagulants, 27(37%) expired while 46(63%) recovered. 8(33.3%) patients on combined anticoagulants expired while 16(66.7%) recovered. 6(8.1%) patients on oral anticoagulants expired while 68(91.9%) recovered.
Conclusion: Anticoagulation improves the outcome of COVID-19 patients and oral anticoagulation is better than subcutaneous and combined anticoagulation.
Keywords: COVID-19, anticoagulant, Rivaroxaban, Enoxaparin

INTRODUCTION

The global pandemic of COVID-19 caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has resulted in unprecedented morbidity and mortality. The rising number of affected individuals lead to the conduction of various studies that aim to decipher the mechanisms of the disease and develop effective treatment and preventive strategies. Among such studies, some have shown an association between thromboembolism and COVID 19 which has proved to be an independent factor for worse clinical outcomes according to clinical, laboratory, and autopsy findings[1,2].

Thromboembolism in COVID-19 has been postulated to be the result of overt inflammation; cytokines release from mononuclear cells, along with Complement activation, involvement of von will brand factor and platelets cause pan-endothelitis and procoagulant state[3]. All these pathological events have been collectively termed as COVID-19–associated coagulopathy accounting for elevated laboratory markers of VTE(fibrin, fibrin degradation products, fibrinogen, and D-dimer levels) and clinical deterioration[4,5].

In COVID-19 hospitalized patients, the frequency of macrovascular thrombotic events ranges between 10-30%. Apart from macro-vascular complications, microvascular events have been found to be vitally important in critical COVID-19 patients. Autopsy findings from several cases have shown microthrombi in small pulmonary vessels showing an association between COVID coagulopathy and multi-organs dysfunction including acute respiratory distress syndrome[6,7].

As soon as the COVID coagulopathy was identified as one of the deteriorating factors, the use of anticoagulation was introduced in COVID-19 patients. Anticoagulants, particularly Heparins are known to have anti-inflammatory effects along with their anticoagulant functions. There is an overlap between the immune system and thrombosis formation and heparin not only abates thrombin formation but also mitigates inflammatory response by binding to the inflammatory cytokines and inhibiting leukocyte migration and neutrophil chemotaxis as mentioned in multiple publications[8]. This quality makes heparin very useful in the treatments of COVID-associated coagulopathy which is thought to result from overt inflammation[9]. Anticoagulants use in COVID-19 patients has been observed to be associated with reducing thrombotic complications in several studies[10].

This recognition led to the use of prophylactic anticoagulation in COVID-19 hospitalized patients in multiple centers. Also, randomized trials were initiated to determine the optimal anticoagulant regimen with regard to the dosing, choice of medicine, route of administration and duration of treatment. Some of these trials compared the use of therapeutic versus prophylactic doses of anticoagulation in terms of improved survival[11]. Similarly, there is a lack of evidence regarding the use of oral versus subcutaneous anticoagulants.

In our study, we have determined the effects of anticoagulants by comparing the morbidity and mortality in patients who were and were not given anticoagulation, also we compared the efficacies of oral anticoagulants, subcutaneous anticoagulants, or combined.

METHODS

This is a retrospective cohort study. The study was conducted at a leading private-sector hospital in Lahore, Pakistan. The hospital has a 20-bed dedicated COVID floor and a 5 bedded COVID ICU. Hospital ethical committee approval was gained before data collection. All adult patients of all genders presenting to the study hospital with confirmed COVID-19 on PCR test or with a radiological diagnosis of COVID-19 from 1st April 2020 to 30 Sep 2020 were included. Patients with known thromboembolic

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disorders were excluded. Data were collected retrospectively through electronic and paper patient records. The data was de-identified in order to preserve patient confidentiality.

Oral anticoagulation was Novel Oral Anticoagulants (NOACS)- Rivaroxaban 10mg once daily while subcutaneous anticoagulation was (low-molecular-weight heparin- clexane 40mg Subcutaneous once-daily dosing). Some patients were given a combination of anticoagulants I-e subcutaneous followed by oral. A combination of anticoagulants was used in patients who were unable to take the tablets orally, either due to being too unwell or having an unsafe swallow. These patients were changed to oral anticoagulants as soon as they were able to take oral medication.

Thrombosis refers to the formation of blood clots in the blood vessels. When this clot breaks from its site of origin and travels through the blood to other places, it is called thromboembolism[12].

Ethics: Hospital ethics committee approval, patient data was de-identified

Statistics: Data were entered into Microsoft Excel and analyzed using SPSS version 24.0. Frequency tables were generated for all possible variables and the Chi-square test was applied to find an association between categorical variables. *A p*-value of <0.05 was considered significant.

RESULTS

A total of 179 eligible patients were included in the study among which 96(53.6%) were male patients while 83(46.4%) were female patients. 145(81%) patients had co-morbid conditions which include: Pregnant=2(1.1%), Diabetes Mellitus=94(52.5%), Hypertension=105(58.7%), heart diseases=50(27.9%), renal disease= 15(8.4%), lung disease/smoker= 12(6.7%). 34(19%) patients had no co-morbid conditions. The number of patients on oxygen was 26(14.5%). The total number of patients who expired is 42(23.5%), while 137(76.5%) patients recovered from the disease (Table 1).

Table 1: Overall patient characteristics (n=179)

Variable	n=	Percentage (%)
Males	96	53.6%
Females	83	46.4%
Pregnant	2	1.1%
Diabetes Mellitus	94	52.5%
Hypertension	105	58.7%
Heart Disease	50	27.9%
Renal Disease	15	8.4%
Lung disease/smoker	12	6.7%
No co-morbids	34	19%
Expired	42	23.5%
Recovered	137	76.5%

Patients on anticoagulants versus no anticoagulants: The total number of patients that were given anticoagulants was 172(100%) among which 41(23.8%) were expired while 131(76.2%) recovered from the disease. 7(100%)patients were not given any form of anticoagulation among which 1(14.3%) patient expired while 6(85.7%)recovered from the disease.

Progression toward invasive ventilation: A total of 20(11.2%) patients progressed toward the need for invasive ventilation among which 1 (14.3%) patient was not given anticoagulation while 19(11%) patients were given anticoagulation. A total of 152 (89.0%) patients did not progress towards invasive ventilation among which 6 (85.7%) patients did not receive any form of anticoagulation while 159 (88.8%) patients received some form of anticoagulation. This is shown in table 2.

Table 2; Progression to Invasive Ventilation

	Progression to Invasive Vent	No progression
Anticoagulants	19 (11.0%)	152 (89.0%)
No Anticoagulants	1 (14.3%)	6 (85.7%)
Total	20 (11.2%)	159 (88.8%)
P value	1.00	

Oral versus subcutaneous versus combination anticoagulants: A total of 74(100%) patients were given oral anticoagulation (NOACS- Rivaroxaban 10mg once daily), among which 6(8.1%) patients expired while 68(91.9%) recovered from the disease.

A total of 73(100%) patients were given subcutaneous anticoagulation (low-molecular-weight heparin- clexane 40mg Subcutaneous once-daily dosing), among which 27(37%) were expired while 46(63%) recovered from the disease. A total of 24(100%) patients were given a combination of anticoagulants (oral plus subcutaneous), among which 8(33.3%) were expired while 16(66.7%) recovered from the disease (Table 3).

Table 3: Comparison of expired and recovered patients

	Expired	Recovered	Total	P value
Oral Anticoagulant	6 (8.1%)	68 (91.9%)	74(100%)	p= 0.00
Subcutaneous anticoagulants	27 (37%)	46 (60%)	73(100%)	p= 0.00
Combination	8(33.3%)	16 (66.7%)	24(100%)	p= 0.220

DISCUSSION

In 2019, the world was struck by a COVID-19 pandemic by the SARS-CoV-2 virus whose clinical manifestations ranged from mild respiratory illness to severe life-threatening pneumonia, (13) acute respiratory distress syndrome, sepsis, and death. Later on, an association was found between thromboembolism and COVID 19 resulting in other manifestations of the diseases like intra-vascular microthrombi, especially in the pulmonary vasculature, venous and arterial thromboembolism, and cardiovascular disease[14-16].

A number of studies postulate a relationship between worse clinical outcomes and COVID-19 coagulopathy[17,18] that led to the use of anticoagulants in the disease with the view of improving clinical outcomes. (8) Later on, the use of anticoagulants in COVID-19 was found to be associated with decreased mortality[19]. According to Multiple observational studies, improvement was observed in the clinical outcome of COVID-19 hospitalized patients who were given a prophylactic dose of Enoxaparin in terms of improved survival and intubation freedom[20].

In our study, 172 patients were given anticoagulation. They showed improvement in the clinical outcomes with only 11.1% progressing toward the need for invasive ventilation while 88.8% did not. This can be compared to the patients who were not on any anticoagulation among which 14.3% progressed towards the need for invasive ventilation which is more than the patients who received anticoagulation.

A large cohort study of 2,773 patients in the Mount Sinai Health System in New York City showed improved mortality in patients who were given anticoagulation. Also, patients who were already on mechanical ventilation showed reduced mortality with the use of anticoagulation compared to their counterparts[21].

Likewise, Improved mortality rates were also postulated in another comparative observational study of 4,297 COVID-19 hospitalized veteran patients among which some were given anticoagulation while others did not receive any[22].

A Chinese study of 449 patients with severe COVID-19 and high D- dimer levels also showed improved mortality rates with anticoagulation as compared to no anticoagulation[5].

Similarly, the benefits of anticoagulation were also demonstrated in a retrospective cohort study of 3,625 patients in the united states[23].

So our study resonates with the previous studies which show decreased mortality and morbidity of COVID-19 patients with the use of anticoagulants. Along with studying the benefits of anticoagulation versus no anticoagulation, we also tried to find out answers to other queries that rose with the progressive use of anticoagulation in COVID-19 patients as to what optimal regimen should be used for anticoagulation, the choice of agents, their routes, doses, and duration of the treatment.

We analyzed the efficacies of oral, subcutaneous, and combined anticoagulation in our study. We have compared three groups of patients who were either given oral or subcutaneous agents or the ones who were given a combination of oral and subcutaneous anticoagulants. Our results showed that oral anticoagulants are better than subcutaneous and combined as only 8.1% of patients who were on oral agents expired while 91.9% recovered. This can be compared with 37.0% and 33.3% of patients who expired on subcutaneous and combined anticoagulation respectively which is more than that of the oral. Many other studies showed variable results as some showed better results with subcutaneous agents while few showed better results with oral agents[24,25].

Multiple other centers also initiated trials to monitor the output and possible complications using different regimens and to find out the optimal regimen[2,26].

Some studies favor the use of oral anticoagulants while others do not. Rivaroxaban was proven to be more effective than Enoxaparin in mild to moderate COVID-19 in one study[24].

Meanwhile, in another trial, no added benefit was observed for the use of a therapeutic dose of oral Rivaroxaban when compared to the prophylactic dose of heparin[25].

Use of oral therapeutic-dose Rivaroxaban and other direct oral anticoagulants was advised to be avoided after the results of a multicenter, randomized, controlled trial, in Brazil in which therapeutic versus prophylactic anticoagulation (oral and subcutaneous)was compared[27].

The results of our study here do not resonate with the results of some other studies. It could be because of the reason that many COVID-19 patients with severe illness are in the ICU and cannot be given oral medicines. we also faced similar limitations as most of the patients who came to the hospital were suffering from severe illness and were admitted to the ICU and could only be given subcutaneous anticoagulation.

CONCLUSION

According to this study, only 11.1% of patients who were given anticoagulation progressed toward the need for invasive ventilation which suggests that anticoagulation improves the outcome of COVID-19 patients as compared to no anticoagulation. Results also showed that 8.1% of patients on oral anticoagulants expired which is less than those given subcutaneous or combined anticoagulation, 37%, and 33.3% respectively. Our study suggests that the outcome of COVID-19 patients improves with anticoagulation, while oral anticoagulation is better than subcutaneous and combined anticoagulation. Limitations to our study are; most of the patients who came to the hospital were suffering from severe illness and were admitted to the ICU and could only be given subcutaneous anticoagulation. More studies are needed to evaluate the efficacies of different anticoagulant regimens.

Recommendation: Large-scale randomized controlled trials are needed to evaluate the optimal regimen.

Conflicts of interest: None declared

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Ethical Approval: The study was approved by the hospital Institutional Review Board.

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