MCBU SBED
MANİSA CELAL BAYAR ÜNİVERSİTESİ SAĞLIK BİLİMLERİ ENSTİTÜSÜ DERGİSİ
MANISA CELAL BAYAR UNIVERSITY JOURNAL OF INSTITUTE OF HEALTH SCIENCE
ISSN: 2147-9607

ARAŞTIRMA MAKALESİ
RESEARCH ARTICLE
CBU-SBED, 2022, 9(1): 106-111

Antikoagülan Tedavi ve COVID-19

Anticoagulant Treatment and COVID-19

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Gönderim Tarihi / Received:10.10.2021
Kabul Tarihi / Accepted: 27.10.2021
DOI: 10.34087/cbusbed.1007918

Öz

Giriş ve Amaç: Bu çalışmada, atriyal fibrilasyonun (AF) COVID-19 hastalarında mortaliteye etkisini ve riskli AF hastalarının belirlenmesinde kullanılabilicek risk skorlarını incelemeyi amaçladık. Bunun yanında oral antikoagülan kullanımın tedavideki yerini incelemeyi amaçladık.

Gereç ve Yöntemler: COVID-19 tanısı almış hastaların kayıtları retrospektif olarak incelendi. Bu hastalar içinden AF tanısı olan 48 hasta belirlendi. Hastaların yoğun bakım ihtiyacı, mortalitesi, CHA_2DS_2VASC ve HAS-BLED skorları kaydedildi. CRP ve D-Dimer düzeyleri kaydedildi. Hastaların kullanmış oldukları oral antikoagülan tedaviler kayıt altına alındı.

Bulgular: Yoğun bakım ünitesinde takip edilen hastaların CHA_2DS_2VASC (yoğun bakım: 4,50±1,41, dahiliye servisi: 2,50±1,05, p<0,05) ve HAS-BLED (yoğun bakım: 2,0±1,08, dahiliye servisi: 1,5±0,77, p<0,05) skorları daha yüksekti. Hayatını kaybeden atriyal fibrilasyonlu hastalar daha yüksek CRP (hayatta kalan: 21,50 ± 15,23, hayatta kalmayan: 142,30 ± 48,49, p <0,05) ve D-Dimer (hayatta kalan: 183,47 ± 43,68, hayatta kalmayan: 878,98 ± 112,24, p <0,05) değerlerine sahipti. Hastaların 24'ü kullanmış olduğu oral antikoagülana devam ederken 24'ü düşük molekül ağrlıklı heparin (DMAH) kullanmış. Bu hastaların hiçbirinde kanama saptanmadı. Eritrosit replasmanı gerektiren anemi iki grup arasında benzerdi (oral antikoaülan: 2 (8,3%), DMAH: 3 (12,5%), p:0,152). Mortalite her iki grup arasında benzerdi (oral antikoaülan: 5 (20,8%), DMAH: 5 (20,8%), p:0,248).

Sonuç: AF, COVID-19'da mortaliteyi etkileyen önemli bir kardiyovasküler risk faktörüdür. Riskli hastaların belirlenmesinde CHA_2DS_2VASC ve HAS-BLED skorları önemlidir. CRP ve D-Dimer, riskli AF hastalarının belirlenmesinde önemli laboratuvar parametreleridir. Hastaların kullanmış oldukları antikoagülan tedaviler COVID-19 tedavisinde önerilen DMAH yerine düşünülebilir.

Anahtar kelimeler: Antikoagülan tedavi, Atriyal fibrilasyon, COVID-19, CHA_2DS_2VASC, HAS-BLED.

Abstract

Objective: In this study, we aimed to examine the effect of atrial fibrillation (AF) on mortality in COVID-19 patients and the risk scores that can be used in determining risky AF patients. In addition, we aimed to examine the place of oral anticoagulant use in treatment.

Materials and Methods: Records of patients diagnosed with COVID-19 were retrospectively reviewed. Among these patients, 48 patients with a diagnosis of AF were identified. Intensive care need, mortality, CHA_2DS_2VASC and HAS-BLED scores of the patients were recorded. CRP and D-Dimer levels were recorded. Oral anticoagulant treatments used by the patients were recorded.

Results: The CHA_2DS_2VASC (intensive care: 4,50±1,41, internal medicine service: 2,50±1,05, p<0,05) and HAS-BLED (intensive care: 2,0±1,08, internal medicine service: 1,5±0,77, p<0,05) scores of the patients followed in the intensive care unit were higher. Non-Survivor Patients with atrial fibrillation had higher CRP (survivor: 21,50±15,23, non-survivor: 142,30±48,49, p<0,05) and D-Dimer (survivor: 183,47±43,68, non-survivor: 878,98±112,24, p<0,05) values. While 24 of the patients continued their oral anticoagulant use, 24 of them used low molecular weight heparin

(LMWH). No bleeding was detected in any of these patients. Anemia requiring erythrocyte replacement was similarbetween the two groups (oral anticoagulant: 2 (8,3%), LMWH: 3 (12,5%), p:0,152). Mortality was similar between both groups (oral anticoagulant: 5 (20,8%), LMWH: 5 (20,8%), p: 0,248).
Conclusion: AF is an important cardiovascular risk factor affecting mortality in COVID-19. CHA2DS2VASC and HAS-BLED scores are important in determining patients at risk. CRP and D-Dimer are important laboratory parameters in determining risky AF patients. Anticoagulant treatments used by patients can be considered instead of LMWH recommended in the treatment of COVID-19.

Keywords: Anticoagulant treatment, Atrial Fibrillation, COVID-19, CHA2DS2VASC, HAS-BLED.

1. Introduction

On December 31, 2019, the World Health Organization (WHO) reported cases of pneumonia of unknown etiology in Wuhan City, Hubei Province, China [1]. On January 7, 2020, a new type of coronavirus (new coronavirus, nCoV) was detected that caused these cases of pneumonia. Due to phylogenetic similarity to the severe acute respiratory syndrome coronavirus (SARS-CoV), the new virus has been named SARS-CoV-2. WHO announced that the official name of the new coronavirus is COVID-19 [2]. As the number of cases spread around the world, the World Health Organization declared a pandemic on March 11, 2020 [3].

COVID-19 predominantly affects the respiratory system. However, existing cardiovascular disease and cardiovascular risk factors have been observed to increase vulnerability to COVID-19 and have been found to increase mortality [4,5]. In Italy, atrial fibrillation (AF) was detected in 19% of 99 patients hospitalized for COVID-19 and in 26% of patients with cardiovascular risk factors. AF was observed more especially in those with high mortality [6]. In another study, 75% of geriatric patients hospitalized for COVID-19 had a past medical history of AF [7]. As known, AF is the most common arrhythmia affecting 1-2% of the population and is associated with increased stroke, heart failure and death. The most important mortality reducing treatment is anticoagulation [8-10]. On the other hand, COVID-19 can be complicated by coagulopathy due to systemic inflammation and diffuse intravascular coagulation (DIC) may occur in most of the deaths [5,11,12]. Anticoagulant therapy has been recommended for COVID-19 patients by some expert consensus. [13]. After that the International Thrombosis and Hemostasis Association (ISTH) recommends that all hospitalized COVID-19 patients be given a prophylactic dose of low molecular weight heparin (LMWH) [14]. Atrial fibrillation (AF) and oral anticoagulant therapy, which are an important cause of cardiovascular morbidity and mortality, were ignored in the studies. The follow-up of patients with AF and therefore receiving oral anticoagulant treatment, the interaction of drugs used in the treatment of COVID-19 and anticoagulant treatment, and their mortality are unknown.

In our study, we aimed to evaluate the relationship between AF and mortality. We tried to determine the importance of oral anticoagulant therapy in the treatment of COVID-19. For this purpose, we evaluated the bleeding and cerebrovascular accident risk scores of the patients.

2. Materials and Methods

2.1 Study design

The research protocol complies with the Declaration of Helsinki and was approved by Celal Bayar University Medicine Faculty Non-Interventional Clinical Trials Ethics Committee (decision no: 85252386-050.04.04-24.08.2020). Every patient/legal representative signed a written informed consent, accepting the procession of personal data for scientific purposes at the moment of hospital admission.

The study was designed as a single center, retrospective, and observational. Merkezefendi State Hospital, which functions as the study center pandemic hospital, was determined. The data of patients hospitalized between 30 May and 1 October 2020 were removed from the electronic medical records and 48 patients who received anticoagulant therapy for atrial fibrillation were identified. The COVID-19 diagnosis of the patients was confirmed by PCR test. Age, gender and cardiovascular risk factors of the patients were recorded. Drugs used in the treatment of COVID-19 were recorded. Patients being followed up in intensive care conditions were recorded. Patients' kidney function tests, c-reactive protein (CRP) levels, whole blood test, coagulation parameters and D-Dimer levels, which is a fibrin degradation product, were recorded. It was recorded whether the patients had bleeding and cerebrovascular accident. The mortality of the patients was recorded. CHA_2DS_2VASC (C: Congestive heart failure, H: Hypertension, A2: Age (≥75 years), D: Diabetes Mellitus, S2: Prior Stroke or TIA or thromboembolism (2 point), A: Age (65–74 years), Sc: Sex category (i.e. female sex)) and HAS-BLED (H: Hypertension, A: Abnormal renal and liver function, S: Stroke, B: Bleeding, L: Labile INR, E: Elderly, D: Drugs or alcohol) scores of the patients were calculated.

2.2 Statistical Analysis of Data

Percentage-frequency analysis was applied to determine the distribution of the participants according to descriptive characteristics. Mean and standard deviation values were calculated to examine the ages of the patients, CHA_2DS_2VASC, HAS-BLED, urea, creatinine, glomerular filtration rate (GFR), aspartate transaminase (AST), alanine transaminase (ALT), C-reactive protein (CRP), haemoglobin (HGB), hematocrit (HCT), international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT) and D-DIMER scores.

The Mann-Whitney U test was used to compare the length of stay of the patients, CHA_2DS_2VASC and and D-DIMER scores according to their mortality status. Data were analyzed using SPSS 24.0. The confidence level was determined as 95% and $p < 0.05$ values were considered statistically significant.

3. Results and Discussion

3.1. Results

48 patients diagnosed with AF were included in the study. The mean age of the patients was found to be 72,45 ± 11,84 years. The 19 (39,6%) patients were female. The most common symptom was fever (77,08%). Cough (64,58%) and shortness of breath (20,83%) followed. Diarrhoea (4,17%), muscle ache (4,17%), fatigue and iredness (12,5%) were less common symptoms. Hypertension (56,25%) was found to be the most common cardiovascular risk factor. Less frequent diabetes mellitus (27,08%), Chronic heart failure (33,33%) and coronary artery disease (22,91%) were found. Chronic obstructive pulmonary disease (6,25%) and hyperlipidemia (10,41%) were the least common cardiovascular risk factors. Eighteen of the patients (37,5%) needed intensive care (Table 1).

Table 1. Baseline characteristics of study population

	Patients with Atrial Fibrilation (n:48)
Age, years	72,45±11,84
Female sex, n (%)	19 (39,6)
Symptoms at admission, n (%)	
Fever	37 (77,08)
Cough	31 (64,58)
Shortness of breath	10 (20,83)
Diarrhoea	2 (4,17)
Fatigue, tiredness	6 (12,5)
Muscle ache	2 (4,17)
Comorbidities	
Diabetes mellitus	13 (27,08)
Hypertension	27 (56,25)
Coronary artery disease	11 (22,91)
Chronic heart failure	16 (33,33)
Chronic obstructive pulmonary disease	3 (6,25)
Hyperlipidemia	5 (10,41)
Need for intensive care unit (n, %)	18 (37,5)

When the laboratory values are examined, urea (mg / dl) (7,.40 ± 58,00), serum creatinine (mg / dl) (1,30 ± 0,96), glomerular filtration rate (mL / min / 1,73 m2) (61,33 ± 26,25), aspartate transaminase (u / l) (60,58 ± 95,91), alanine transaminase (u / l) (36,05 ± 46,47), C-reactive protein (mg / dl) (87,65 ± 105,13), D-dimer (ng / ml) (813,78 ± 1416,04), prothrombin time (sec) (17,04 ± 7,65), activated partial thromboplastin time (sec) (35,03 ± 10,72), international normalized ratio (1,39 ± 0,41), haemoglobin (g / dl) (11,48 ± 1,79), hematocrit (%) (35,35 ± 5,11). All patients were using Hydroxychloroquine (100%). 29 of the patients (60,41%) were using Azithromycin and 7 of the patients (14,58%) were using Favipiravir (Table 2).

The CHA_2DS_2VASC (intensive care: 4,50±1,41, internal medicine service: 2,50±1,05, $p<0,05$) and HAS-BLED (intensive care: 2,0±1,08, internal medicine service: 1,5±0,77, $p<0,05$) scores of the patients followed in the intensive care unit were higher (Table 3).

Table 2. Laboratory parameters and medications

	Patients with Atrial Fibrilation (n:48)
Laboratory parameters	
Urea, mg/dl	71,40±58,00
Serum creatinine, mg/dl	1,30±0,96
Glomerular filtration rate, mL/min/1.73 m^2	61,33±26,25
Aspartate transaminase, u/l	60,58±95,91
Alanine transaminase, u/l	36,05±46,47
C-reactive protein, mg/dl	87,65±105,13
D-dimer, ng/ml	813,78±1416,04
Prothrombin time, sec	17,04±7,65
Activated partial thromboplastin time, sec	35,03±10,72
International normalized ratio (INR)	1,39±0,41
Haemoglobin, g/dl	11,48±1,79
Hematocrit, %	35,35±5,11
Medications, (n, %)	
Hydroxychloroquine	48 (100)
Azithromycin	29 (60,41)
Favipiravir	7 (14,58)

Table 3. CHAD2VASC2 and HAS-BLED score

	Intensive Care (n:18)	Internal Medicine Service (n:30)	p value
CHA_2DS_2VASC	4,50±1,41	2,50±1,05	<0,05
HAS-BLED	2,0±1,08	1,5±0,77	<0,05

Abbreviations: CHA_2DS_2VASC : C:Congestive heart failure, H:Hypertension, A2:Age (≥75 years), D:Diabetes Mellitus, S2:Prior Stroke or TIA or thromboembolism (2 point), A:Age (65–74 years), Sc:Sex category (i.e. female sex) , HAS-BLED: H:Hypertension, A:Abnormal renal and liver function, S:Stroke, B:Bleeding, L:Labile INR, E:Elderly, D:Drugs or alcohol

Non-Survivor Patients with Atrial Fibrillation had higher CRP (survivor: 21,50±15,23, non-survivor: 142,30±48,49, p<0,05) and D-Dimer (survivor: 183,47±43,68, non-survivor: 878,98±112,24, p<0,05) values (Table 4).

Table 4. CRP and D-Dimer levels of Survivors and Non-Survivors with Atrial Fibrillation

	Survivor Patients with Atrial Fibrillation (n:38)	Non-Survivor Patients with Atrial Fibrillation (n:10)	p value
C-reactive protein (CRP)	21,50±15,23	142,30±48,49	<0,05
D-Dimer	183,47±43,68	878,98±112,24	<0,05

While 24 of the patients continued their oral anticoagulant use, 24 of them used low molecular weight heparin (LMWH). No bleeding was detected in any of these patients. Anemia requiring erythrocyte replacement was similar between the two groups (oral anticoagulant: 2 (8,3%), LMWH: 3 (12,5%), p:0,152). Mortality was similar between both groups (oral anticoagulant: 5 (20,8%), LMWH: 5 (20,8%), p: 0,248) (Table 5).

Table 5. Comparison of Oral Anticoagulant Treatment and LMWH Treatment

	ORAL ANTICOAGULANT TREATMENT	LMWH TREATMENT	p value
Bleeding	0	0	-
Need for ERT	2 (8,3%)	3 (12,5%)	0,152
Mortality	5 (20,8%)	5 (20,8%)	0,248

Abbreviations: ERT: erythrocyte replacement therapy, LMWH: low molecular weight heparin

3.2. Discussion

In our study, mortality was found to be high in patients with high CHA2DS2VASC and HAS-BLED scores. It was observed that as the CRP and D-Dimer levels increased, mortality increased. There was no difference in bleeding, need for erythrocyte replacement therapy (ERT) and mortality between the groups using oral anticoagulants and using low molecular weight heparin (LMWH).

Atrial fibrillation is the most common arrhythmia and patients with AF can be treated by hospitalization for COVID-19. There is no study on which AF patients will have high mortality. Anticoagulant therapy is the most important mortality reducing treatment in AF patients [9]. COVID-19 can be complicated by coagulopathy due to systemic inflammation and diffuse intravascular coagulation (DIC) can occur in most of the deaths. Therefore, anticoagulant drugs are recommended in the treatment of COVID-19, such as AF [14]. The recommended treatment is LMWH. However, patients using oral anticoagulant therapy for AF remain unclear. Should these patients continue on oral anticoagulant therapy or should they use LMWH? When we analyzed it retrospectively, we found that half of the patients included in the study continued their oral anticoagulant treatments. These patients were using new generation oral anticoagulant drugs (rivaroxaban, apixaban, dabigatran, edoxaban) and vitamin K antagonist (warfarin sodium). When we compared these patients with the patients using LMWH, we did not find any significant difference in terms of bleeding, need for ERT and mortality. Although not as much as heparin, it may cause heparin-induced thrombocytopenia in LMWH [15]. Oral anticoagulant therapy does not have this risk. In addition, the oral route may be preferred instead of the subcutaneous treatment method, which is painful for anticoagulant treatment. Close monitoring is recommended in patients receiving oral anticoagulant therapy, as there may be an interaction with antiretroviral drugs used in the treatment of COVID-19 [16]. In our study, 7 patients were receiving antiviral therapy. These patients did not use any oral anticoagulants. LMWH was used in these patients. No bleeding or cerebrovascular accident was observed in the patients. Testa et al. On April 15, 2020, they switched from oral anticoagulation to parenteral heparin in hospitalized patients with SARS-CoV-2 [17]. They explained that the reason for the replacement of oral anticoagulants with parenteral heparin was the increased prothrombin time (PT) / INR instability in patients hospitalized with COVID due to high vitamin K metabolism, diet, liver failure, and heart failure. Considering the pharmacological properties of oral anticoagulant drugs, the multiple pharmacological interactions associated with the treatment of acute disease, and the possible need for mechanical ventilation with hospitalization in intensive care units, they recommended the replacement of oral anticoagulant therapies with parenteral [17]. The main reason for this is that they think that intravenous heparin and LMWH use will be easier to follow than oral anticoagulant therapy. There is no biochemical parameter to monitor oral anticoagulant treatments other than warfarin sodium. Heparin follow-up can be done with activated partial thromboplastin time (aPTT) and LMWH can be followed with anti-Xa. The use of anti-Xa is not available in many centers. Blood collection from the patient at regular intervals for aPTT follow-up causes an increase in the risk of healthcare workers in COVID-19, where patient contact should be low. In addition, the application of an easy method such as oral therapy in COVID-19 patients who do not need intensive care seems to be more comfortable for healthcare professionals than intravenous heparin or subcutaneous LMWH. Intravenous heparin and LMWH may be preferred in patients who need intensive care. Biochemical parameters and risk scores can be used to identify patients in need of intensive care. CRP is an acute phase reactant. It is known that high serum CRP levels are associated with increased adverse outcome in patients with COVID, including mortality, severe COVID-19, ARDS, and the need for ICU care [18]. Another biomarker that is an important indicator of mortality in COVID-19 patients is D-Dimer [19]. D-dimer, which was evaluated early, is thought to be a useful marker to improve the management of Covid-19 patients. We found high CRP and D-Dimer levels in AF patients with high mortality. Especially those with high CHA_2DS_2VASC and HAS-BLED scores were more prominent. The CHA_2DS_2VASC and HAS-BLED scores can be used to predict early mortality of patients. These scorings, which help identify patients at risk, can be used to guide intensive therapy with early respiratory support and/or immunosuppressive agents or steroids. There are data showing that this treatment

principle reduces mortality [20]. In our study, we did not find a significant difference between oral anticoagulant use and LMWH use. In patients who do not need intensive care, oral therapy with less contact with the patient may be preferred. In addition, we found that scoring systems are effective in identifying patients in need of intensive care. In these patients, LMWH, which is easier to administer, can be preferred compared to heparin.

Study Limitations

Our study have several limitations. Retrospective nature and relatively small patient population are major limitations.

4. Conclusion

AF is an important cardiovascular risk factor affecting mortality in COVID-19. Anticoagulant therapy is important in the treatment of COVID-19 as well as in the treatment of AF. Oral anticoagulant therapy may also be preferred instead of LMWH in the selection of anticoagulant therapy. Oral therapy can be considered to reduce the health worker's contact with COVID-19, especially in patients who do not need intensive care. CHA_2DS_2VASC and HAS-BLED scores are important in determining patients at risk. CRP and D-Dimer are important laboratory parameters in determining risky patients. Future studies using larger data sets will enable our findings to be validated.

5. Acknowledgements and Disclosures

Conflict of interest: None declared

Peer-review: Externally peer-reviewed

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