Turkish Journal of Thoracic and Cardiovascular Surgery 2024;32(1):37-45

ORIGINAL ARTICLE / ÖZGÜN MAKALE

Anticoagulation strategy with bivalirudin plus aspirin combination during extracorporeal membrane oxygenation for COVID-19-associated acute respiratory distress syndrome

COVID-19'a bağlı akut solunum sıkıntısı sendromu nedeniyle ekstrakorporeal membran oksijenasyonu sırasında bivalirudin-aspirin kombinasyonu ile antikoagülasyon stratejisi

Halide Oğuş, A. Ece Altınay, Hakan Hançer, Mustafa Mert Özgür, Mine Şimşek, Şirin Menekşe, Mustafa Emre Gürcü, Mehmet Kaan Kırali

Department of Cardiovascular Surgery, Koşuyolu High Specialization Training and Research Hospital, Istanbul, Türkiye

ABSTRACT

Background: In this study, we present our experience in treating patients receiving extracorporeal membrane oxygenation for novel coronavirus disease-2019 (COVID-19)-associated acute respiratory distress syndrome using a combined anticoagulant and antiaggregant treatment with intravenous infusion of bivalirudin and aspirin.

Methods: Between April 1st, 2020 and January 31st, 2022, a total of 52 adult patients (32 males, 20 females; mean age: 44.5±11.5 years; range, 21 to 71 years) who received extracorporeal membrane oxygenation due to COVID-19-associated acute respiratory distress syndrome and whose anticoagulant treatment consisted of bivalirudin plus aspirin were retrospectively analyzed. During the first 10 days of extracorporeal membrane oxygenation, bivalirudin dosing, activated partial thromboplastin time, and activated clotting time, as well as major bleeding events and patient and/or ECMO-circuit thromboses were recorded.

Results: The mean bivalirudin dose per day ranged from 0.03 to 0.04 mg/kg/h, with a mean overall dose of 0.036 mg/kg/h. The mean activated partial thromboplastin time was 49.1±6.9 sec throughout 10 days of the application. The percentage of time in the target range for activated partial thromboplastin time was 58.9±20.1% within 10 days of application, compared to 33.1±31.1% for the first 24 h. The mean daily activated clotting time was below the target range within the first three days, but it was consistently within the target range after Day 3. During the first 10 days of the application, no mortality occurred. Major bleeding occurred in 11 patients (21.1%) and circuit thrombosis occurred in three patients (5.8%).

Conclusion: In patients receiving extracorporeal membrane oxygenation for COVID-19-associated acute respiratory distress syndrome, an hourly bivalirudin dose of 0.03 to 0.04 mg/kg/h throughout the first 10 days of application was associated with the targeted anticoagulation profile of 45 to 60 sec. The combination was associated with a comparable rate of major bleeding, but a lower rate of circuit-thrombosis compared to the literature reports.

Keywords: Aspirin, bivalirudin, blood coagulation, COVID-19, extracorporeal membrane oxygenation.

ÖZ

Amaç: Bu çalışmada intravenöz bivalirudin ve aspirin infüzyonu ile kombine antikoagülan ve antiagregan tedavisi kullanılarak yeni koronavirüs hastalığı-2019 (COVID-19) ile ilişkili akut solunum sıkıntısı sendromu nedeniyle ekstrakorporeal membran oksijenasyonu verilen hastalara ilişkin deneyimimiz sunuldu.

Çalışma planı: 1 Nisan 2020 - 31 Ocak 2022 tarihleri arasında COVID-19 ile ilişkili akut solunum sıkıntısı sendromu nedeniyle ekstrakorporeal membran oksijenasyon uygulanan ve antikoagülasyon için bivalirudin ve aspirin verilen toplam 52 erişkin hasta (32 erkek, 20 kadın; ort. yaş: 44.5±11.5 years; dağılım, 21-71 yıl) retrospektif olarak incelendi. Ekstrakorporeal membran oksijenasyonunun ilk 10 günü süresince bivalirudin dozu, aktive parsiyel tromboplastin zamanı, aktive pıhtılaşma zamanı ve majör kanama olayları ve hasta ve/veya ECMO-devre trombozları kaydedildi.

Bulgular: Günlük ortalama bivalirudin dozu 0.03-0.04 mg/kg/saat olup, 10 günlük ortalama doz 0.036 mg/kg/saat idi. Uygulamanın 10 günlük süresince ortalama aktive parsiyel tromboplastin zamanı 49.1±6.9 sn. idi. Aktive parsiyel tromboplastin zamanının hedef aralıkta bulunduğu zaman yüzdesi ilk 24 saatte 33.1±31.1%, uygulamanın 10 günlük süresince ise 58.9±20.1% idi. Ortalama günlük aktive pıhtılaşma zamanı, ilk üç gün içinde hedef aralığın altındaydı; ancak sonraki günlerde hedef aralıkta kaldı. Uygulamanın ilk 10 günü içinde, mortalite görülmedi. Majör kanama 11 hastada (%21.1) ve devre trombozu üç hastada (%5.8) gözlendi.

Sonuç: COVID-19 ile ilişkili akut solunum sıkıntısı sendromu nedeniyle ekstrakorporeal membran oksijenasyonu uygulanan hastalarda, uygulamanın ilk 10 günü içinde 0.03-0.04 mg/kg/saat dozunda bivalirudin 45-60 saniyelik hedef antikoagülasyon değerlerini sağladı. Bu kombinasyon, literatür verileriyle karşılaştırıldığında, benzer majör kanama oranı, ancak daha düşük devre trombozu oranı ile ilişkiliydi.

Anahtar sözcükler: Aspirin, bivalirudin, kan pıhtılaşması, COVID-19, ekstrakorporeal membran oksijenasyonu.

Corresponding author: Halide Oğuş.
E-mail: halideogus66@gmail.com

Doi: 10.5606/tgkdc.dergisi.2024.25230

Received: June 05, 2023
Accepted: October 31, 2023
Published online: January 29, 2024

Cite this article as: Oğuş H, Altınay AE, Hançer H, Özgür MM, Şimşek M, Menekşe Ş, et al. Anticoagulation strategy with bivalirudin plus aspirin combination during extracorporeal membrane oxygenation for COVID-19-associated acute respiratory distress syndrome. Turk Gogus Kalp Dama 2024;32(1):37-45. doi: 10.5606/tgkdc.dergisi.2024.25230.

Coronavirus disease-2019 (COVID-19) affects multiple systems and is usually associated with hypercoagulation and formation of microthrombi, resulting in microvascular thrombosis, venous thromboembolism or acute arterial thrombosis.[1]

Patients with COVID-19 may require extracorporeal membrane oxygenation (ECMO) due to COVID-19-associated pneumonia and severe acute respiratory distress syndrome (ARDS). COVID-19 has also been associated with an increased pro-inflammatory response and pro-thrombotic potential.[2] In patients with COVID-19-associated ARDS, venovenous ECMO (vv-ECMO) is the last resort to keep the patient alive after unsuccessful attempts with less invasive therapeutic options, to allow cell/tissue regeneration or as a bridge to lung transplantation. However, ECMO may be complicated by multiple factors, in particular hypercoagulation and ECMO-circuit thrombosis, making anticoagulant treatment the mainstay in ECMO. Insufficient or excessive anticoagulation or possible complications of anticoagulants may disrupt the artificial circulation and cause failure of the ECMO system. Achievement of target anticoagulation parameters without causing bleeding or thrombosis is particularly challenging due to COVID-19-associated coagulopathy, adverse effects of ECMO or ensuing sepsis.[1]

Although heparin is the most common anticoagulant used in ECMO, it has several drawbacks such as the development of heparin resistance, heparin-induced thrombocytopenia and individual variations in anticoagulation response.[3,4]

Bivalirudin is a direct inhibitor of thrombin.[5] It binds to circulating thrombin, as well as to fibrin-bound thrombin, interfering with the transformation of fibrinogen to fibrin.[5,6] It has been shown to have stable pharmacokinetics, a rapid anticoagulant effect, easy dose titration, and no risks for thrombocytopenia,[5] rendering it advantageous over heparin.[7-9] As an anticoagulant, it has been reported to be as effective as or even safer than heparin in elective percutaneous coronary interventions (PCIs).[10] It has also become a preferred anticoagulant over heparin in some ECMO centers.[8] The use of bivalirudin has been reported in patients receiving ECMO for severe COVID-19-associated ARDS.[11-13] The use of antiplatelet agents including aspirin, ticagrelor or cangrelor has been reported in combination with heparin[14] or bivalirudin[15] to mitigate pro-thrombotic potential of various settings.

In this study, we aimed to present our experience in treating patients receiving ECMO for COVID-19-associated ARDS with a combined anticoagulant and antiaggregant treatment with intravenous infusion of bivalirudin and aspirin during ECMO applications.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at the ICU of Koşuyolu High Specialization Training and Research Hospital between April 1st, 2020 and January 31st, 2022. We reviewed electronic medical records and patients' charts to identify patients who were admitted to the intensive care unit (ICU) with COVID-19-associated ARDS and received vv-ECMO. During the pandemic, our 58-bed cardiovascular ICU served as a member of the Extracorporeal Lung Support Organization (ELSO) not only to patients who were admitted to the ICU, but also to those who were transferred to our center after initiation of ECMO. All patients received anticoagulant treatment with intravenous infusion of bivalirudin combined with 150 mg of daily aspirin. During the pandemic period, none of the patients admitted for COVID-19 received heparin for anticoagulation while on ECMO.

Exclusion criteria included the presence of any of the following conditions: non-COVID-19-associated ARDS, use of left ventricular assist device, use of ECMO for less than 10 days, viral infections other than COVID-19, or intracranial hemorrhage. Data of one patient was unavailable, also requiring exclusion. A total of 52 patients (32 males, 20 females; mean age: 44.5±11.5 years; range, 21 to 71 years) were included. Data included patients' demographic characteristics (age, sex), body weight, coexisting renal replacement therapy, and blood transfusions. All ECMO applications for COVID-19-associated ARDS were managed and supervised by a dedicated ICU team involving cardiovascular surgeons and ICU physicians.

Definitions

COVID-19-associated ARDS was diagnosed based on the Berlin criteria.[16] Obesity was defined as having a body mass index (BMI) of greater than 30 kg/m^2. Chronic respiratory disease was defined as the presence of chronic obstructive pulmonary disease, asthma or any respiratory insufficiency requiring oxygen support.

Laboratory parameters

For anticoagulation, intravenous infusion of bivalirudin was initiated in combination with aspirin on the first ECMO day. Coagulation parameters

monitored throughout the first 10 days of ECMO included activated partial thromboplastin time (aPTT) measured on a Stago STA-R Evolution® analyzer (Diagnostica Stago, NJ, USA) every 4 h within the first 24 h and subsequently every 6 h; activated clotting time (ACT) measured using an i-STAT Kaolin ACT cartridge (Abbott, IL, USA) on an i-STAT 1 analyzer 300-G (Abbott, IL, USA) every 2 h within the first 24 h and subsequently every 4 h; international normalized ratio (INR) measured (Diagnostica Stago) every 4 h within the first 24 h and subsequently every 6 h. Platelet counts were obtained daily. D-dimer and fibrinogen levels were also monitored every two days. Data on hourly bivalirudin doses for each patient and routine ACT monitoring were recorded manually.

Based on the institutional practice, the main target for aPTT was 45 to 60 sec (reference range, 26-35 sec). The target ACT was 170 to 200 sec. The bivalirudin dose was hourly recorded and adjusted, when necessary, mainly based on aPTT, also taking ACT, INR, and the platelet count into consideration; therefore, for each increase of 10 sec in the target aPTT, a corresponding decrease (10 to 25%) in the bivalirudin dose. The percentage of time at which aPTT remained at the target range and the percentage of time at which aPTT was below 45 sec and exceeded 60 sec were calculated for each patient and overall means were obtained for the first 10 days of ECMO. The percentage of time at which aPTT remained at the target range was also calculated for the first 24 h. In the presence of major bleeding accompanied by a platelet count of <50,000 cells, platelets were transfused. In the presence of ongoing bleeding and an INR of >1.5, fresh frozen plasma and/or vitamin K were administered; in the presence of a low fibrinogen level (<1.5 mg/dL), human fibrinogen concentrate was administered. In the presence of persistent bleeding, the bivalirudin dose was consistently reduced in a range of 20%.

ECMO management

All cannulations were performed percutaneously using the right internal jugular vein and the right or left femoral vein. Heparin-coated ECMO systems were used; i.e., LivaNova (LivaNova - Sorin Group Italia s.r.l., Mirandola, Italy) and or Maquet (Getinge Group, Göteborg, Sweden). During the first 10 days of ECMO, only the LivaNova system was used. The size of the cannulas was determined according to the ELSO guidelines. During ECMO, flow and fresh-gas-flow parameters were recorded every hour. For maintenance, each ECMO oxygenator was insufflated with a sweep gas flow at a rate of 10 L/min two times daily. Morning and evening partial oxygen pressures were checked in blood gas samples obtained from the ECMO outflow circuit. The only indication for device-oxygenator replacement was ECMO-circuit thrombosis, defined by any decrease in the partial oxygen pressure below 200 mmHg, while the fraction of inspired oxygen (FiO_2) was 100% in the outflow circuit on two successive measurements. Spare oxygenators were always kept available for the possibility of ECMO thrombosis.

Despite the ECMO duration ranged from 11 to 99 days, the duration for data analysis was set as the first 10 days of ECMO due to the fact that extension of ECMO support beyond 10 days would have caused decreases in the number of patients enrolled.

Weaning from ventilator

During the ECMO support, patients received pressure-controlled ventilation. Following discontinuation of ECMO support and sedatives, patients whose spontaneous respiration was restored continued to have mechanical ventilation in the continuous positive airway pressure (CPAP) mode and, then, were weaned successfully.

Complications

Major bleeding was defined as a decreased hemoglobin level by >2 g/dL due to gastrointestinal or bronchial bleeding, hematuria or intrathoracic hemorrhage detected on chest radiography or computed tomography (CT) or intracranial hemorrhage detected by CT.[16] Any condition indicative of major bleeding was dealt with by adjustment for bivalirudin dosing combined with the use of hemostatic agents or packed red cell transfusions (>1 U) or any intervention to prevent bleeding. Thromboembolic events included ECMO-circuit thrombosis, cerebrovascular ischemia and venous thrombosis confirmed by Doppler ultrasonography.

Statistical analysis

Statistical analysis was performed using the SPSS version 28.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median and interquartile range (IQR), or number and frequency. All parameters were first calculated per day for each patient as means and, then, an overall mean was calculated for the relevant variable. Percentage of aPTT in therapeutic range was calculated by the number of aPTT tests within the therapeutic range divided by the number of total aPTT test, multiplied by 100. Normality of the variables was tested

using the Kolmogorov-Smirnov test. Quantitative independent variables were compared using the independent samples t-test and Mann-Whitney U test. Qualitative independent variables were compared using the chi-squared test or Fisher exact test. In very few cases with missing variables, the pertinent data was removed. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 52 patients, except for one patient, all patients were transferred to our center after initiation of ECMO at another center, with clinical and radiological findings of and a positive polymerase chain reaction (PCR) test for COVID-19. At the time of ICU admission, ACT was in a range of 150 to 170 sec in all patients. Demographic and clinical characteristics of the patients are summarized in Table 1.

The mean daily bivalirudin doses and corresponding coagulation parameters recorded during the first 10 days of ECMO are presented in Table 2. The mean bivalirudin doses per day

Table 1. Demographic, clinical and laboratory characteristics of 52 patients

	n	%	Mean±SD	Range
Age (year)			44.5±11.5	21-71
Sex				
Male	32	61.5		
Female	20	38.5		
Mean weight (kg)			90.6±20.1	60-150
Body mass index (>30 kg/m^2)	21	40.3	30.47±6.12	
The first 10 days of ECMO				
Bivaluridin dose (mg/kg/h)			0.036±000	0.03-0.04
Laboratory parameters				
aPTT (sec) during 10 days			49.1±6.9	
Percentage of aPTT				
At target (45-60 sec) range within the first 24 h (%)			33.1±31.1	
At target range during 10 days (%)			58.9±20.1	
At <45 sec during 10 days (%)			30.1±23.8	
At >60 sec during 10 days (%)			10.6±16.6	
ACT (sec)			162.9±10.6	
Platelet count (×10^3 per μL)			103.8±39.6	
INR			1.4±0.2	
Fibrinogen (mg/dL)			389.8±71.3	
D-dimer (ng/mL)			7.6±4.6	
Hemofiltration	3	5.7		
Due to renal failure	1	1.9		
Cytokine filtration	2	3.8		
Major bleeding	11	21.1		
Bacterial/fungal infections	42	80.8		
ECMO-circuit thrombosis	3	5.8		
Throughout the whole ICU stay				
ICU stay (day)			64.2±32.2	17-156
ECMO duration (day)			45.1±22.4	11-99
In-hospital mortality	22	42.3		

SD: Standard deviation; ECMO: Extracorporeal membrane oxygenation; aPTT: Activated partial thromboplastin time; ACT: Activated clotting time; INR: International normalized ratio; ICU: Intensive care unit.

ranged from 0.03 to 0.04 mg/kg/h. The overall mean bivalirudin dose was 0.036 mg/kg/h.

The mean aPTT was 49.1±6.9 sec throughout 10 days of ECMO. While the mean percentage of time at which aPTT was within the target range was considerably low (33.1±31.1%) for the first 24 h of ECMO, it almost doubled to 58.9±20.1% throughout 10 days of ECMO. The mean percentages of time at which aPTT was below or over the target range were 30.1±23.8% and 10.6±16.6%, respectively. The mean ACT per day was consistently within the target range after Day 3. The mean INR ranged from 1.4 to 1.6. The lowest platelet count was 78×10^3 cells/μL. The mean 10-day D-dimer level was 7.6±4.6 ng/mL.

During the first 10 days of ECMO, no mortality occurred. Major bleeding occurred in 11 patients (21.1%) of bronchial (n=3), bronchial + nasal (n=1), anal fissure (n=1), gastrointestinal (n=3), nasopharyngeal (n=3) source. Major bleeding lasted one day in seven patients, two days in three patients, and five days in one patient.

Extracorporeal membrane oxygenation-circuit thrombosis occurred in three patients (5.8%) (Table 1), on Day 5 (n=1) and on Day 8 (n=2). Two incidences of ECMO-circuit thrombosis coincided with increased administration of blood products due to major bleeding.

Comparison of patients with and without major bleeding showed only INR and D-dimer being significantly higher in patients with major bleeding (Table 3). The percentages of aPTT within, below or over the target range during 10 days of ECMO were similar in the two groups.

The overall mean ICU stay was 64.2±32.2 (range, 17 to 156) days, of which a mean of 45.1±22.4 (range, 11 to 99) days was spent on ECMO (Table 1). The overall mortality rate during hospitalization was 42.3%.

DISCUSSION

In the current study, in which bivalirudin in combination with aspirin was used in place of heparin to manage anticoagulation during vv-ECMO in patients with COVID-19-associated ARDS, an hourly bivalirudin dose of 0.03 to 0.04 mg/kg/h throughout the first 10 days of ECMO was associated with the targeted anticoagulation profile of 45 to 60 sec, yielding a mean aPTT of 49.1±6.9 sec. The percentage of time in the target range for aPTT was 58.9±20.1% within 10 days of ECMO, compared to 33.1±31.1% for the first 24 h. Bivalirudin and aspirin were used

Table 2. Daily bivalirudin doses and coagulation parameters

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Bivalirudin	0.030±0.03	0.038±0.03	0.038±0.03	0.040±0.03	0.040±0.03	0.037±0.03	0.037±0.03	0.035±0.03	0.033±0.03	0.031±0.03
aPTT (sec)	44.1±10.2	45.1±8.1	46.6±7.4	48.2±6.2	49.3±7.2	50.0±7.2	51.1±7.8	51.7±6.7	52.3±7.4	52.8±7.9
ACT (sec)	155±30	155±26	159±30	163±31	164±29	155±26	155±26	155±26	165±29	155±26
Platelet count ($\times10^3$ per μL)	170±77	137±61	115±50	102±40	90±41	83±41	79±39	81±38	78±37	90±44
INR	1.6±0.5	1.5±0.2	1.4±0.2	1.4±0.2	1.4±0.4	1.4±0.3	1.4±0.3	1.4±0.2	1.4±0.2	1.4±0.2

SD: Standard deviation; aPTT: Activated partial thromboplastin time; ACT: Activated clotting time; INR: International normalized ratio.

Table 3. Inter-group comparisons of patients with and without major bleeding

	No major bleeding (n=41)					Major bleeding (n=11)					
	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Age (year)			44.0±12.1					45.8±10.3			0.61¶
Sex											0.92*
Male	14					6					
Female	22					10					
Mean weight (kg)			92.6±21.1					86.2±17.5			0.26§
				The first 10 days of ECMO							
Bivaluridin dose (mg/kg/h)				0.03	0.02-0.05				0.03	0.02-0.04	0.32§
Coagulation parameters											
aPTT during 10 days (sec)			49.6±8.5					47.5±7.0			0.30¶
Percentage of aPTT during 10 days											
At target (45-60 sec) range (%)				63	52.3-77.3				61.0	42.1-74.7	0.46§
At <45 sec (%)				25.6	11-41				35	11.9-65.9	0.32§
At >60 sec (%)				2.6	0-21.2				0	0-10	0.24§
ACT (sec)			152.3±22.1					161.4±23.9			0.78¶
Platelet count ($\times 10^3$ per μL)			100.4±55.6					107.8±60.7			0.52¶
INR			1.3±0.3					1.7±0.4			0.04¶
Fibrinogen (mg/dL)				316	201-495				368	256-481	0.20§
D-dimer (ng/mL)				4.5	2.4-8.1				7.7	4.6-18.6	0.03§
Blood product transfusions											
Fresh frozen plasma (U)			7.1±2.8					8.8±3.5			0.094§
Pooled platelets (U)			0.8±1.1					1.1±1.4			0.43§
Apheresis platelets	1	2.8				3	18.7				0.081*
Cryoprecipitate	1	2.8				0	0				1.00*
Infections	26	72.2				16	100				0.019*
ECMO-circuit thrombosis	1	2.8				2	12.5				0.221*
				Throughout the whole ICU stay							
ICU stay (day)			62.0±32.3					69.3±32.7			0.462 ¶
ECMO duration (day)			43.7±21.8					48.3±24.1			0.53 ¶
In-hospital mortality	16	44.4				6	37.5				0.640*

SD: Standard deviation; IQR: Interquartile range; aPTT: Activated partial thromboplastin time; ACT: Activated clotting time; INR: International normalized ratio; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; § Mann-Whitney U-test; * Chi-squared test (Fisher's exact test); ¶ Independent samples t-test.

together to obtain both anticoagulant and antiplatelet effects, respectively. Adverse events included major bleeding (21.1%) and ECMO-circuit thrombosis (5.8%).

Due to the known drawbacks of heparin during ECMO,[4,17] interest is growing in the use of bivalirudin as an alternative in either dedicated ECMO centers[18] or sporadically.[19] To date, only a single center has reported a dosing protocol for anticoagulation with bivalirudin to monitor and guide coagulation parameters.[20] There has been a growing number of reports on the use of bivalirudin, with varying target anticoagulation parameters and ensuing complications in patients with or without COVID-19-associated ARDS.[11,21] In another study comparing bivalirudin and heparin in critically ill patients with severe COVID-19, bivalirudin displayed similar rates of hospital mortality and thromboembolic complications.[22]

In the current study, we aimed to provide a 10-day dosing picture for bivalirudin, with corresponding target anticoagulation parameters. Our target aPTT was relatively lower than rates reported in the literature. Trigonis et al.[11] achieved a target aPTT of 60 to 80 sec with a median bivalirudin dose of 0.18 mg/kg/h in 19 patients receiving ECMO for COVID-19-associated ARDS. In another report of 33 COVID-19 patients on ECMO, a starting bivalirudin dose of 0.2 mg/kg/h provided a therapeutic range of 60 to 80 sec for aPTT within an average of 20 h.[21] Seelhammer et al.[19] reported a 27-day course of ECMO in a patient with COVID-19, during which a target aPTT range of 60 to 80 sec was achieved with a bivalirudin dose of 0.15 to 0.25 mg/kg/h, with no occurrence of ECMO-circuit thrombosis. Our target anticoagulation parameters, particularly aPTT, and the bivalirudin doses were lower than those reported for ECMO applications both in COVID-19 and non-COVID-19 patients.[7,11] Aspirin may have had a role in reducing bivalirudin doses.

Patients with and without major bleeding differed significantly in only two laboratory parameters; i.e., INR and D-dimer being higher in the former group. In case of a higher INR (≥1.5), we administered fresh frozen plasma and/or vitamin K. We could not explain why the D-dimer levels were significantly higher in patients with major bleeding, for which no literature data could be found in patients with COVID-19.

In the current study, aspirin was used to mitigate the potential pro-thrombotic effect of COVID-19.[2] The use of aspirin with bivalirudin was also reported in patients with or without COVID-19 during ECMO, *albeit* in a small proportion of patients (11%).[11] A systematic review and meta-analysis that compared bivalirudin or argatroban with heparin in patients on ECMO reported significantly lower rates of in-hospital mortality, major bleeding and pump-related thrombosis and higher time percentages within the therapeutic range with bivalirudin or argatroban.[23] In our study, during the first 10 days of ECMO, no patients developed venous or arterial thrombosis, and ECMO-circuit thrombosis was detected on three devices. The absence of venous or arterial thrombosis in our study with bivalirudin plus aspirin is in contrast with the findings of Trigonis et al.[11] who reported deep venous thrombosis in 57.9% of COVID-19 patients receiving ECMO for a median of 11 days and who reported no data on the replacement of oxygenators or occurrence of ECMO-circuit thrombosis. In our study, all ECMO oxygenators were used beyond the validation period indicated by the manufacturer as five days, until the occurrence of ECMO-circuit thrombosis. Thus, the three incidences of ECMO-circuit thrombosis occurred on Day 5 (n=1) and Day 8 (n=2), which coincided with increased administration of blood products due to major bleeding in two patients. Our combination strategy might have led to a lower rate of ECMO-circuit thrombosis (5.8%) over the first 10 days of ECMO compared to 26.3% within seven days of ECMO[24] and 17.3% in a study that used bivalirudin alone.[25]

The use of an antiplatelet agent in combination with anticoagulant treatment has rarely been reported, the results of which have been comparable to anticoagulant treatment alone or even better with the combination. Bein et al.[14] compared heparin-receiving patients with and without low-dose aspirin during pumpless extracorporeal lung assist for an average of 6.6 days. The addition of aspirin did not increase bleeding events or the need for transfusion. In another study, Baldetti et al.[15] used cangrelor in combination with bivalirudin during venoarterial ECMO in patients undergoing PCI. During a mean of five days of combined anticoagulation treatment, a thrombotic event occurred in 14%, and major bleeding occurred in 21% patients.

The main limitation to our study is its retrospective design and lack of a comparison group; therefore, it may only provide limited evidence about the use of bivalirudin plus aspirin for anticoagulation. Another limitation is that we could not evaluate the effect of aspirin on

thrombocyte function due to the unavailability of tests to monitor platelet function, such as bedside thromboelastography. Activated clotting time monitoring was performed using the i-STAT ACT test, which is less sensitive to low-dose heparin than the Hemochron low-range ACT (ACT-LR) test.

In conclusion, in patients receiving extracorporeal membrane oxygenation for COVID-19-associated acute respiratory distress syndrome, an hourly bivalirudin dose of 0.03 to 0.04 mg/kg/h throughout the first 10 days of extracorporeal membrane oxygenation was associated with the targeted anticoagulation profile of 45 to 60 sec. In addition, the combination was associated with a comparable rate of major bleeding and a lower rate of circuit-thrombosis as compared with the literature reports.

Ethics Committee Approval: The study protocol was approved by the Kartal Kosuyolu High Specialization Training and Research Hospital Ethics Committee (date: 09.08.2022, no: 2022/11/601). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conception, design, collection and analysis of data, drafting, revising, approval: H.O.; Analysis of data, approval of the final form: A.E.A., H.H., M.M.Ö., M.Ş., Ş.M., M.E.G.; Conception , design, and analysis of data, approval of the final form: M.K.K.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-7. doi: 10.1016/j.thromres.2020.04.013.
2. Gorog DA, Storey RF, Gurbel PA, Tantry US, Berger JS, Chan MY, et al. Current and novel biomarkers of thrombotic risk in COVID-19: A Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. Nat Rev Cardiol 2022;19:475-95. doi: 10.1038/s41569-021-00665-7.
3. Levy JH, Connors JM. Heparin resistance - clinical perspectives and management strategies. N Engl J Med 2021;385:826-32. doi: 10.1056/NEJMra2104091.
4. Neunert C, Chitlur M, van Ommen CH. The changing landscape of anticoagulation in pediatric extracorporeal membrane oxygenation: Use of the direct thrombin inhibitors. Front Med (Lausanne) 2022;9:887199. doi: 10.3389/fmed.2022.887199.
5. White CM. Thrombin-directed inhibitors: Pharmacology and clinical use. Am Heart J 2005;149(1 Suppl):S54-60. doi: 10.1016/j.ahj.2004.10.023.
6. McMichael ABV, Ryerson LM, Ratano D, Fan E, Faraoni D, Annich GM. 2021 ELSO adult and pediatric anticoagulation guidelines. ASAIO J 2022;68:303-10. doi: 10.1097/MAT.0000000000001652.
7. Pieri M, Agracheva N, Bonaveglio E, Greco T, De Bonis M, Covello RD, et al. Bivalirudin versus heparin as an anticoagulant during extracorporeal membrane oxygenation: A case-control study. J Cardiothorac Vasc Anesth 2013;27:30-4. doi: 10.1053/j.jvca.2012.07.019.
8. Taylor T, Campbell CT, Kelly B. A review of bivalirudin for pediatric and adult mechanical circulatory support. Am J Cardiovasc Drugs 2021;21:395-409. doi: 10.1007/s40256-020-00450-w.
9. Hasegawa D, Sato R, Prasitlumkum N, Nishida K, Keaton B, Acquah SO, et al. Comparison of bivalirudin versus heparin for anticoagulation during extracorporeal membrane oxygenation. ASAIO J 2023;69:396-401. doi: 10.1097/MAT.0000000000001814.
10. Xiang DC, Gu XL, Song YM, Huang WJ, Tang LQ, Yin YH, et al. Evaluation on the efficacy and safety of domestic bivalirudin during percutaneous coronary intervention. Chin Med J (Engl) 2013;126:3064-8.
11. Trigonis R, Smith N, Porter S, Anderson E, Jennings M, Kapoor R, et al. Efficacy of bivalirudin for therapeutic anticoagulation in COVID-19 patients requiring ECMO support. J Cardiothorac Vasc Anesth 2022;36:414-8. doi: 10.1053/j.jvca.2021.10.026.
12. Kırali K, Erkılınç A, Erdal Taşçı A, Mert Özgür M, Gecmen G, Altınay E, et al. Follow-up strategy with long-term veno-venous extracorporeal membrane oxygenation support for complicated severe acute respiratory distress related to COVID-19 and recovery of the lungs. Turk Gogus Kalp Damar Cerrahisi Derg 2021;29:252-8. doi: 10.5606/tgkdc.dergisi.2021.21208.
13. Lorusso R, De Piero ME, Mariani S, Di Mauro M, Folliguet T, Taccone FS, et al. In-hospital and 6-month outcomes in patients with COVID-19 supported with extracorporeal membrane oxygenation (EuroECMO-COVID): A multicentre, prospective observational study. Lancet Respir Med 2023;11:151-62. doi: 10.1016/S2213-2600(22)00403-9.
14. Bein T, Zimmermann M, Philipp A, Ramming M, Sinner B, Schmid C, et al. Addition of acetylsalicylic acid to heparin for anticoagulation management during pumpless extracorporeal lung assist. ASAIO J 2011;57:164-8. doi: 10.1097/MAT.0b013e318213f9e0.
15. Baldetti L, Nardelli P, Ajello S, Melisurgo G, Calabrò MG, Pieri M, et al. Anti-thrombotic therapy with cangrelor and bivalirudin in venoarterial extracorporeal membrane oxygenation patients undergoing percutaneous coronary intervention: A single-center experience. ASAIO J 2023;69:e346-50. doi: 10.1097/MAT.0000000000001871.

16. ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: The Berlin Definition. JAMA 2012;307:2526-33. doi: 10.1001/jama.2012.5669.
17. Demma LJ, Winkler AM, Levy JH. A diagnosis of heparin-induced thrombocytopenia with combined clinical and laboratory methods in cardiothoracic surgical intensive care unit patients. Anesth Analg 2011;113:697-702. doi: 10.1213/ANE.0b013e3182297031.
18. Pappalardo F, Agracheva N, Covello RD, Pieri M, De Bonis M, Calabrò MG, et al. Anticoagulation for critically ill cardiac surgery patients: Is primary bivalirudin the next step? J Cardiothorac Vasc Anesth 2014;28:1013-7. doi: 10.1053/j.jvca.2013.10.004.
19. Seelhammer TG, Rowse P, Yalamuri S. Bivalirudin for maintenance anticoagulation during venovenous extracorporeal membrane oxygenation for covid-19. J Cardiothorac Vasc Anesth 2021;35:1149-53. doi: 10.1053/j.jvca.2020.06.059.
20. Netley J, Roy J, Greenlee J, Hart S, Todt M, Statz B. Bivalirudin anticoagulation dosing protocol for extracorporeal membrane oxygenation: A retrospective review. J Extra Corpor Technol 2018;50:161-6.
21. Bissell BD, Gabbard T, Sheridan EA, Baz MA, Davis GA, Ather A. evaluation of bivalirudin as the primary anticoagulant in patients receiving extracorporeal membrane oxygenation for SARS-CoV-2-associated acute respiratory failure. Ann Pharmacother 2022;56:387-92. doi: 10.1177/10600280211036151.
22. Pieri M, Quaggiotti L, Fominskiy E, Landoni G, Calabrò MG, Ajello S, et al. Anticoagulation strategies in critically ill patients with SARS-CoV-2 infection: The role of direct thrombin inhibitors. J Cardiothorac Vasc Anesth 2022;36:2961-7. doi: 10.1053/j.jvca.2022.03.004.
23. M'Pembele R, Roth S, Metzger A, Nucaro A, Stroda A, Polzin A, et al. Evaluation of clinical outcomes in patients treated with heparin or direct thrombin inhibitors during extracorporeal membrane oxygenation: A systematic review and meta-analysis. Thromb J 2022;20:42. doi: 10.1186/s12959-022-00401-2.
24. Kaseer H, Soto-Arenall M, Sanghavi D, Moss J, Ratzlaff R, Pham S, et al. Heparin vs bivalirudin anticoagulation for extracorporeal membrane oxygenation. J Card Surg 2020;35:779-86. doi: 10.1111/jocs.14458.
25. Rivosecchi RM, Arakelians AR, Ryan J, Murray H, Ramanan R, Gomez H, et al. Comparison of anticoagulation strategies in patients requiring venovenous extracorporeal membrane oxygenation: Heparin versus bivalirudin. Crit Care Med 2021;49:1129-36. doi: 10.1097/CCM.0000000000004944.