Efficacy of bivalirudin for therapeutic anticoagulation in COVID-19 patients requiring ECMO Support

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Objectives:

The COVID-19 pandemic has been associated with cases of refractory acute respiratory distress syndrome (ARDS) sometimes requiring support with extracorporeal membrane oxygenation (ECMO). Bivalirudin can be used for anticoagulation in patients on ECMO support, but its efficacy and safety in patients with COVID-19 is unknown. We set out to compare the pharmacologic characteristics and dosing requirements of bivalirudin in patients requiring ECMO support for ARDS due to COVID-19 versus ARDS from other etiologies.
Design and Setting:

This retrospective case control study was performed at Indiana University Health Methodist Hospital in Indianapolis, IN.

Participants:

Patients were included if they were on veno-venous (VV) ECMO support between June 2019 and June 2020 and divided into two groups: ARDS secondary to COVID-19 and those with ARDS from another etiology (Non-COVID).

Interventions:

Patient demographics such as age, sex, weight, chronic comorbid conditions, baseline antiplatelet and anticoagulant use, antiplatelet use during ECMO, and need for renal replacement therapy were collected and compared between groups. Time to activated partial thromboplastin time (aPTT) goal, percentage of time at aPTT goal, bivalirudin rates, total bivalirudin requirements, total duration on bivalirudin, total duration on ECMO, mortality, and complications associated with ECMO were collected and compared between groups.

Measurements and Main Results:

A total of forty-two patients met inclusion criteria (n = 19 COVID-19, n = 23 Non-COVID). However, percentage of aPTTs at goal were maintained more consistently in patients with COVID-19 versus non-COVID (86% vs. 74%; p < 0.01). Higher median (IQR) daily rates (3.1 mCg/kg/min (2.3-5.2) vs. 2.4 mCg/kg/min (1.7-3.3): p = 0.05) and higher median (IQR) maximum rates of bivalirudin (5 mCg/kg/min (3.7-7.5) vs. 3.8 mCg/kg/min (2.5-5): p = 0.03)
were required in the COVID-19 group versus the non-COVID group. Time to goal aPTT was similar between groups. There was no difference in complications associated with anticoagulation as demonstrated by similar rates of bleeding and thrombosis between both groups.

Conclusions:
Patients on ECMO with ARDS from COVID-19 require more bivalirudin overall and higher rates of bivalirudin to maintain goal aPTTs compared to patients without COVID-19. However, COVID-19 patients more consistently maintain goal aPTT. Future randomized trials are needed to support efficacy and safety of bivalirudin for anticoagulation of COVID-19 patients on ECMO.

Introduction

The coronavirus 2019 (COVID-19) pandemic has been associated with severe SARs-CoV-2 pneumonia and subsequent development of severe acute respiratory distress syndrome (ARDS), at times refractory to standard mechanical ventilation. Rescue therapy with extracorporeal membrane oxygenation (ECMO) is often considered for severe SARs-CoV-2 pneumonia with ARDS. Support of COVID-19 patients with ECMO presents many clinical challenges. COVID-19 infection has been associated with an increased prothrombotic state resulting in increased incidence of arterial and venous thrombi [1]. This unique physiologic state occurring in patients infected with COVID-19 combined with the intrinsically prothrombotic nature of ECMO makes the use of systemic anticoagulation in this patient population imperative [2].
Unfractionated heparin is the most used anticoagulant in the United States for ECMO due to physician familiarity, availability, cost-effectiveness, and ease of reversal. Despite its popularity, heparin comes with its own challenges. Heparin requires binding to antithrombin (AT) to exert its anticoagulant effect. In patients with low AT levels, this leads to heparin resistance, need for antithrombin III supplementation, and the potential for thrombosis. Heparin also binds to plasma proteins including acute phase reactants, which leads to fluctuations in aPTT values and coagulation status [3]. Bivalirudin, a direct thrombin inhibitor, has recently been gaining popularity. Bivalirudin, unlike heparin, inhibits both free circulating and fibrin-bound thrombin. Bivalirudin is a renally cleared agent with a short half-life, which allows for rapid attainment of steady state, rate titration and cessation of anticoagulant effects when necessary. Bivalirudin does not rely on antithrombin III to exert its anticoagulant effect, removing need for costly supplementation, and negates the risk for the development of heparin resistance and heparin-induced thrombocytopenia (HIT) [4]. Bivalirudin is the primary anticoagulant used at our institution for all ECMO patients due to its indirect reduction of costly antithrombin III supplementation and the ability to maintain aPTTs in goal range more consistently than with heparin [5,6]. Bivalirudin has been used for anticoagulation for all COVID-19 patients placed on ECMO support at our institution. Given the novel nature of both this disease and its associated coagulopathy, we set out to collect observational data regarding pharmacologic properties, drug dosing and requirements, and associated outcomes in patients with COVID-19 utilizing anticoagulation with bivalirudin while on ECMO. We hypothesized that given the prothrombotic findings seen in COVID-19 patients, they would require higher dosing regimens of bivalirudin to achieve goal anticoagulation.
Methods

Adult patients 18 years of age and older who were hospitalized at IU Health Methodist Hospital (Indianapolis, IN, USA) requiring veno-venous (VV) ECMO between June 17th, 2019 – June 17th, 2020 were identified through electronic medical records. The Indiana University (IU) Institutional Review Board (IRB) approved the conduct of this study and deemed it exempt (IRB Study Number 2006253636). Informed consent was waived, and de-identified data was analyzed.

Patients were supported using either the Cardiohelp (Maquet) or Centrimag (Abbot) extracorporeal systems. Decision to cannulate for ECMO was determined by a multidisciplinary team of intensivists and cardiovascular surgeons. This decision was multifactorial but primarily dictated by the presence of presumed reversible hypoxic or hypercarbic respiratory failure refractory to traditional management. Secondary factors considered on a case-by-case basis included age, comorbidities, and presence of other organ system failures. Patients were excluded from this study if they required veno-arterial (VA) ECMO or other ventricular support devices. Patients were also excluded if VV ECMO was utilized in the immediate post-operative period following lung transplantation or for respiratory failure secondary to trauma. Bivalirudin was dosed in all patients by in-house pharmacists who were monitoring values 24-hours per day at our institution.

Age, sex, weight in kilograms (kg), chronic comorbid conditions, need for renal replacement therapy (RRT) after initiation on ECMO, use of antiplatelet agents or therapeutic anticoagulation prior to cannulation, antiplatelet use during ECMO, as well as in-hospital and on-ECMO
mortality were recorded. Comorbidities collected included obesity, cardiovascular disease, chronic respiratory disease, chronic kidney disease, and diabetes mellitus. Obesity was defined as body mass index (BMI) greater than 30 kg/m². History of cardiovascular disease was defined as hypertension, coronary artery disease, or congestive heart failure. Chronic kidney disease was defined as abnormalities of kidney function, present for greater than 3 months, documented by a reduction of glomerular filtration rate <60 ml/min/1.73 m². Chronic respiratory disease history included chronic obstructive pulmonary disease, asthma, or chronic respiratory failure requiring supplemental oxygen use.

Our primary outcomes of total daily bivalirudin requirement and highest daily rate of bivalirudin infusion (both in mcg/kg/min) were obtained via manual chart review. Our secondary outcomes of incidence of bleeding and thrombotic events as well as the proportion of aPTT measurements within the defined goal range for the individual patient, were also collected. Bleeding events were defined as acute blood loss requiring acute transfusion and thrombotic events were defined as deep venous thromboses diagnosed on ultrasound evaluation. Specific bleeding events were subsequently categorized as intracranial bleeding as diagnosed on cross-sectional imaging and gastrointestinal bleeding as diagnosed on bedside exam or endoscopic evaluation. Transfusions were performed according to providers judgement with usual criteria being a hemoglobin less than 7 g/dL or an acute blood loss with associated hemodynamic changes. Cessation of bivalirudin was also provider directed with no defined protocol but generally only performed in the setting of acute bleeding. Ultrasounds were performed routinely on all patients successfully decannulated from ECMO. Total cost of bivalirudin was also calculated for each patient.
The goal aPTT ranges utilized in this analysis are consistent with the pre-COVID-19 targets at this center which was 60 – 80 seconds. Our institutional protocol for bivalirudin dosing while on ECMO is defined in Table 1.

Baseline variables with normal distributions were described as mean and standard deviation and as median and interquartile ranges (IQR) for data with skewed distribution. Continuous variables were compared using Mann-Whitney U test and categorical measures through Pearson chi-square test or Fisher exact test. P values of <0.05 were defined as statistically significant. All analyses were performed using SPSS Statistics 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY).

Results

Forty-two patients requiring VV ECMO for ARDS were included for analysis (n = 42), 19 patients in the COVID-19 group and 23 patients non-COVID group. Among patients in the non-COVID-19 group, bacterial pneumonia and viral influenza were the most common causes of respiratory failure, each accounting for 30.4% of cases as displayed in Table 2. Demographic, clinical, and complication data is shown in Table 3. The groups were well matched with regards to age, sex, comorbidities, and utilization of RRT. However, patients in the COVID-19 group were noted to have higher baseline weight (98.0 kg vs 87.1 kg, p = 0.04) compared to the non-COVID-19 group but had no difference in rate of obesity (74% vs 52%, p = 0.21). There was also no difference noted in rate of aspirin use prior to cannulation nor while on ECMO (13% vs 11%, p = 1.00 and 13% vs 11%, p = 0.61, respectively). No patients in either group were on
other antiplatelet agents prior to cannulation or while on ECMO. Therapeutic anticoagulation use prior to cannulation was also not statistically different (9% vs 0%, p = 0.49). Finally, there was also no significant difference with in-hospital mortality between the groups (22% vs 16%, p = 0.71) or mortality while patients were on ECMO (13% vs 16%, p = 1.00).

Clinical data for these patients showed similar total time on ECMO but longer total time spent on bivalirudin in the COVID group (255 hours vs 136 hours, p = 0.03). Maintenance of goal therapeutic aPTT, described as a percentage of time within goal range, was achieved more often in the COVID group (86% vs. 74%, p < 0.01). Patients in the COVID-19 group were found to have higher median daily bivalirudin requirements (3.1mCg/kg/min vs. 2.4mCg/kg/min, p = 0.05), as well as higher maximum rates (5mCg/kg/min vs. 3.8mCg/kg/min, p = 0.025). This also corresponded to a higher overall cost of bivalirudin in the COVID-19 group ($28425 vs $12507, p = 0.01). Patients in the COVID-19 group were also found to have longer ICU length of stay (29 days versus 20 days, p = 0.04) but there was no difference in their overall hospital length of stay (29.5 days versus 24 days, p = 0.17).

There was no difference between groups in the incidence of bleeding events (26.1% vs. 21.1%, p = 0.7) or thrombotic events (39.1% vs. 57.9%, p = 0.23) following initiation of ECMO and systemic anticoagulation with bivalirudin.

Discussion
This is the first known study to assess the pharmacologic characteristics and dosing requirements of bivalirudin in patients requiring ECMO support for COVID-19. In this report, patients on ECMO for ARDS secondary to COVID-19 were more consistently able to maintain aPTTs within goal and were found to require higher median and maximum bivalirudin rate requirements without increased incidence of bleeding or thrombosis.

While heparin remains the most used anticoagulant for patients on ECMO in the United States, bivalirudin use is increasing. While previously being utilized primarily in patients with heparin sensitivities [7], it is becoming an increasingly common first-line anticoagulant. More evidence is coming to light and supporting this shift, finding that it may be associated with decreased circuit-related thrombotic events as well as decreased blood product transfusion [8,9]. Its use in COVID-19 patients has also been described in several case studies [4,10], but has never been compared directly between COVID-19 patients and those with other etiologies of respiratory failure prior to our investigation.

The patients in our study were well matched except for weight. Bivalirudin employs weight-based dosing using total body weight which is supported as the most accurate guide for achieving aPTT goals [11]. Though the overall weight was higher in the COVID-19 patients, the rate of obesity was not different between the groups. The patients spent similar times on ECMO though the large IQR in both groups speaks to the variability of individual patient ECMO runs. There was a significant higher total time spend on bivalirudin in the COVID group as compared to the non-COVID patients. In reviewing the data, this seems to be primarily due to two patients in the non-COVID group who spent prolonged times off bivalirudin during their course due to
significant hemorrhage that was difficulty to control. There were no other cofounders that we believed would have contributed to the difference in the ability to maintain our desired levels of anticoagulation in these patients.

A possible physiologic explanation for aPTTs being more consistent in the COVID-19 group is that there were more heterogeneous pathologies making up the non-COVID group. This heterogeneity may have led to variable effects on both the pharmacokinetics of bivalirudin as well as underlying coagulation disturbances of the disease processes themselves. There was also heightened awareness among providers of the prothrombotic nature of COVID-19 infection which may have driven more stringent scrutiny of aPTT trends and rate titrations.

There are several hypotheses that may explain the higher bivalirudin rate requirement in the COVID-19 group. The first being the development of bivalirudin resistance in this patient population. In non-COVID patients, direct thrombin inhibitor resistance is speculated to be due to elevated factor VIII and fibrinogen as well as large clot burden [12,13]. Hypercoagulability has been documented in COVID-19 patients [14,15] but specific correlation with overall dosing of anticoagulants has not been explored. Patients with COVID-19 have been found to have markedly elevated fibrinogen and factor VIII levels (11). Heparin resistance has been demonstrated in COVID-19 patients and is likely due to increased factor VIII and fibrinogen [16]. When heparin resistance is present, aPTTs are typically seen as a poor marker and other assays such as anti-Xa monitoring is utilized. This increased factor VIII and fibrinogen in COVID-19 patients could also potentially contribute to the higher rates of bivalirudin in the
COVID-19 group however, alternative assays to monitor anticoagulation for direct thrombin inhibitors such as dilute thrombin time and ecarin thrombin time are not readily available [12].

Secondly, COVID-19 patients have also been shown to have an increased incidence of microthrombi [17,18]. Since bivalirudin binds to both free and clot bound thrombin, the increase in microthrombi may have resulted in increased binding sites and an increased concentration necessary for saturation [19]. Further support for this theory is that the patients in the COVID-19 group often required very high bivalirudin rates up front but did not remain at these rates throughout treatment with bivalirudin.

In comparing the clinical courses of these patients, COVID-19 patients were found to have longer ICU durations but similar overall hospital lengths of stay. The ICU duration may be skewed by several variables including time needed for mechanical ventilation both before and after cannulation of ECMO as well as bed availability for patients to transfer to once stable enough to leave the ICU. The latter was particularly notable during the COVID-19 pandemic with high hospital censuses limiting patient movement. The similar hospital lengths of stay however suggest that the differing ICU courses were not as impactful on overall admission duration.

Notably, there were no significant differences in the rates of bleeding or thrombosis in either group. While this does suggest that bivalirudin is safe in these COVID-19 patients at the higher doses they were exposed to, the small number of events in each group also limits more substantial conclusions and may be a target for further research.
There are several strengths of this analysis, the first of which include the institutional utilization of bidirectional infusion pump technology which allowed the investigators to calculate maximum and total bivalirudin infusion rates more accurately. In addition, the use of a 24-hour clinical pharmacist driven bivalirudin dosing service allowed for rapid protocolized bivalirudin rate adjustment. The primary weaknesses of this analysis are the size and single-center nature of our study population. This leads to essential limitations in the statistical and clinical conclusions that can be drawn as well as the generalizability of the findings. Finally, given the retrospective nature of the data collection, it was often difficult to determine when bivalirudin may have been temporarily held for procedures or minor bleeding. While this could have influenced the overall amount of bivalirudin each patient received, it was unlikely to significantly change the results comparing to two groups since the documentation issue occurred in both the COVID and non-COVID groups.

COVID-19 and its associated coagulopathy has been explored extensively in recent literature. In this small retrospective review of patients requiring veno-venous ECMO support, those with respiratory failure secondary to COVID-19 infection required higher median daily and maximum bivalirudin rates as compared to patients without COVID-19 to sustain goal aPTT values. Despite these higher rates, the aPTT values were more consistent in the COVID-19 group and there was no increase in bleeding or thrombotic complications. Further prospective analyses are needed to draw definitive conclusions regarding anticoagulation requirements in COVID-19 patients on veno-venous ECMO support.
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Table 1. Bivalirudin dosing and adjustment protocol for patients on ECMO

| Measured aPTT (seconds) | Dosing Adjustment Protocol                              |
|-------------------------|---------------------------------------------------------|
| < 45                    | Increase infusion rate by 40%                           |
| 45 – 59                 | Increase infusion rate by 20%                           |
| 60 – 80                 | No change to infusion rate                              |
| 81 – 110                | Decrease infusion rate by 20%                           |
| > 110                   | Hold infusion for 1 hour, and then restart with previous rate decreased by 40% |
Table 2. Causes of respiratory failure requiring ECMO support for patients in the non-COVID group (n=23)

| Cause                        | n (%)  |
|------------------------------|--------|
| Bacterial Pneumonia         | 7 (30.4) |
| Viral Influenza              | 7 (30.4) |
| Aspiration                   | 6 (26.1) |
| Asthma Exacerbation          | 2 (8.7)  |
| Unknown                      | 1 (4.3)  |

Table 3. Demographic, clinical, and complication data for patients on therapeutic bivalirudin anticoagulation during ECMO support.

| Demographic                                      | Non-COVID (n = 23) | COVID (n = 19) | p-value |
|--------------------------------------------------|--------------------|----------------|---------|
| Age (years), Median (IQR)                        | 48 (28-52)         | 40 (33-49)     | 0.75    |
| Females, n (%)                                   | 11 (48)            | 6 (32)         | 0.29    |
| Weight (kg), Median (IQR)                        | 87.1 (68.2-99.8)   | 98.0 (87.2-110.1) | 0.04    |
| Obese, n (%)                                     | 12 (52)            | 14 (74)        | 0.21    |
| Hx. Diabetes Mellitus, n (%)                     | 2 (9)              | 5 (26)         | 0.21    |
| Hx. Chronic Kidney Disease, n (%)                | 3 (13)             | 0 (0)          | 0.24    |
| Hx. Cardiovascular Disease                       | 10 (44)            | 5 (26)         | 0.34    |
| Hx. Chronic Respiratory Disease                  | 10 (44)            | 3 (16)         | 0.09    |
| Prior Aspirin Use                                | 3 (13)             | 2 (11)         | 1.00    |
| Aspirin While on ECMO                            | 3 (13)             | 1 (5)          | 0.61    |
| Prior Anticoagulation Use                        | 2 (9)              | 0 (0)          | 0.49    |
| In-hospital Mortality                            | 5 (22)             | 3 (16)         | 0.71    |
| Mortality on ECMO                                | 3 (13)             | 3 (16)         | 1.00    |
| Renal Replacement Therapy after ECMO initiation, n (%) | 6 (26)             | 2 (11)         | 0.20    |

Clinical

| Total Time on ECMO (hours), Median (IQR)         | 167 (136 – 351)    | 263 (165 – 525) | 0.16    |
| Metric                                      | Value 1                     | Value 2                     | p-value |
|---------------------------------------------|------------------------------|----------------------------|---------|
| Total Time on Bivalirudin (hours), Median (IQR) | 136 (79 – 260)              | 255 (160 – 502)             | 0.03    |
| Time to Goal aPTT (hours), Median (IQR)     | 16.4 (5.7-26.5)             | 12.1 (7.79-16.4)            | 0.87    |
| Percentage of aPTT Measurements in Goal (%) | 74.0 (59.5-81.8)            | 86.0 (80.1-90)              | < 0.01  |
| Median Daily Bivalirudin rate (mCg/kg/min), Median (IQR) | 2.4 (1.7-3.3)              | 3.1 (2.3-5.2)               | 0.05    |
| Highest Daily Rate (mCg/kg/min), Median (IQR) | 3.8 (2.5-5)                 | 5 (3.7-7.5)                 | 0.03    |
| Total Cost of Bivalirudin (US Dollars)      | 12507 (3411 – 19329)        | 28425 (13075 – 46617)       | 0.01    |
| ICU Length of Stay (days), Median (IQR)     | 20 (8 – 28.5)               | 29 (16.8 – 36.25)           | 0.04    |
| Hospital Length of Stay (days), Median (IQR) | 24 (13 – 38.5)             | 29.5 (26 – 35.3)            | 0.17    |

### Complications

| Condition                                      | Value 1 (n, %) | Value 2 (n, %) | p-value |
|------------------------------------------------|----------------|----------------|---------|
| Bleeding, n (%)                                | 6 (26)         | 4 (21)         | 0.70    |
| Intracranial or Intraocular Bleeding, n (%)    | 0 (0)          | 0 (0)          | 1.00    |
| Gastrointestinal bleeding, n (%)               | 5 (22)         | 3 (16)         | 0.63    |
| Deep Venous Thrombosis, n (%)                  | 9 (39)         | 11 (58)        | 0.23    |