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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The importance of anticoagulation in COVID-19-related acute kidney injury requiring continuous renal replacement therapy

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SUMMARY

Introduction/Objective In Serbia, the coronavirus disease 2019 (COVID-19) pandemic began in early March 2020.

The aim of this study is to summarize clinical experience in the treatment of COVID-19-associated acute kidney injury by methods of continuous renal replacement therapy (CRRT) with the focus on the amount of the administered dose of unfractionated heparin.

Methods The study covers 12 patients treated with CRRT at the Clinic for Infectious Diseases at the Clinical Center of Vojvodina from March 6 to May 20, 2020. Antithrombotic prophylaxis, risk of venous thromboembolism (VTE), applied therapy, biochemical parameters before and after CRRT, anticoagulation and other CRRT parameters were analyzed.

Results The mean age of the patients was 61.54 ± 10.37 years and seven (58.3%) were men. All the patients received standard thromboprophylaxis. Nine (75%) patients had Padua Prediction Score for Risk of VTE ≥ 4, but none developed a thrombotic event. Seven critically ill patients with multi-organic dysfunction developed acute kidney injury dependent on CRRT. The mean CRRT dose was 36.6 ml/kg/h, the mean bolus dose of unfractionated heparin was 3250 ± 1138.18 IU, and the continuous dose was 1112.5 ± 334.48 IU/kg/h. Discontinuation of CRRT due to the clotting circuit was necessary in only one patient. The values of leukocytes, AST, ALT, GGT, aPTT, PT were significantly higher after CRRT compared to urea, creatinine, potassium, chlorine and magnesium, whose values were significantly lower.

Conclusion In our COVID-19 patients who had high inflammatory parameters and D-dimer and an estimated risk of developing deep vein thrombosis, the implementation pre-dilution continuous veno-venous hemodiafiltration with antithrombotic membrane and $^1/_3$ to $^1/_2$ higher unfractionated heparin doses than the recommended one, the filter life lasted longer with no complications.

Keywords: COVID 19; continuous renal replacement therapy; acute kidney injury; thrombotic events

INTRODUCTION

Acute kidney injury (AKI) is frequently present in the critically ill patients, especially in patients with severe infections and it is related to significant morbidity and mortality rates [1].

A meta-analysis that included 20 journals and 6945 patients showed an 8.9% prevalence of AKI in patients with COVID-19, although statistical heterogeneity between studies was found [2]. According to previous studies, renal replacement therapy (RRT) is required by 25% of severely ill COVID-19 patients [3].

Several studies have shown that the course of COVID-19 can lead to diverse thrombotic complications caused by inflammation, hypoxia, disseminated intravascular coagulation as well as certain study drugs [4]. These drugs can be the cause of severe interactions with antithrombotic therapy or anticoagulants [5].

The most common hemostatic abnormalities in COVID-19 are mild thrombocytopenia and an elevated level of D-dimer, which is related to a higher possibility of the need for mechanical ventilation (MV), ICU admittance or lethal outcome [6]. It is believed that the severity of the disease is linked to a prolonged prothrombin time (PT) and international normalized ratio (INR), thrombin time (TT) and the shortened of activated partial thromboplastin time (aPTT) [4]. The latter consideration refers to the relation of hemostatic changes with the liver dysfunction in COVID-19 patients [7]. An elevated level of D-dimer is likely to cause thrombotic complications in COVID-19 patients [8].

Recent studies have reported the presence of venous thromboembolism (VTE) that are in fact pulmonary embolism found in 16.7–35% patients with cumulative frequency up to 49% in 14 days [9, 10].

Although RRT treatment can be related to a higher bleeding rate, a great prevalence of VTE supports the use of thromboprophylaxis in the absence of active bleeding or a severe thrombocytopenia [11].

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In the cases of AKI, continuous renal replacement therapy (CRRT) is a preferred treatment modality due to its lesser impact on hemodynamic stability and adequate volume control. However, the exposure of blood to the artificial circuit leads to blood clotting and it can cause thrombosis with a greater loss of blood, which results in the additional burdening of medical staff and increased expenses [12]. In order to diminish the risk of circuit thrombosis, regional anti-coagulation with citrate or heparin (unfractionated heparin (UFH) or low molecular weight heparin) or systemic anticoagulation (UFH, low molecular weight heparin, or prostacyclin) are used [13]. In case of frequent circuit clotting, national guidelines published in England suggest the following: vascular approach optimization, considering alternative/combined anticoagulant strategies including combined citrate and heparin (systemic or through circuit), heparin and epoprostenol or argatroban if other prothrombotic disorders are excluded [14].

The aim of this study is to summarize clinical experience in the treatment of COVID-19-associated AKI by modality of CRRT with the focus on the amount of the administered dose of UFH.

METHODS

The study included 276 patients with COVID-19 pneumonia who were treated at the Clinic for Infectious Diseases, Clinical Center of Vojvodina from March, 6 to May, 20 2020. Of those, 12 adult patients were treated with CRRT due to COVID-19-associated AKI. Seven of them (58.3%) developed AKI within multiorgan failure and were treated in ICU, while five (41.7%) were treated in the semi-intensive care unit.

The study has been approved by the competent ethics committee of the Clinical Center of Vojvodina.

We analyzed: demographic data; comorbidities; laboratory and clinical parameters 24 hours before and after CRRT; simplified acute physiology score (SAPS II) and modified early warning score (MEWS); presence of acute respiratory distress (ARDS) and secondary infections; the need for multiple organ support, invasive MV, non-invasive ventilation, high-flow nasal cannula; Padua Prediction Score for Risk of VTE, dose of thromboprophylaxis; onset of CRRT since admission, anuria before CRRT, CRRT modalities, type of adsorptive membrane, dose of CRRT (ml/kg/h), achieved ultrafiltration during CRRT (ml), bolus dose (IU) and continuous dose (IU/kg/h) of UFH during CRRT; number of procedures of CRRT; therapy received by patients, length of hospitalization and mortality.

The SAPS II score consists of 12 physiological variables and three disease-related variables collected in the first 24 hours of admission to the ICU. The SAPS II score may vary between 0 and 163 points (0–116 points for physiological variables, 0–17 points for age and 0–30 points for previous diagnosis). The MEWS score is based on four standard physiological variables and on the AVPU consciousness assessment (warning, voice response, pain response, no response). The primary purpose of the MEWS is to prevent delays in the intervention or transfer of the critically patients. A score ≥ 5 is statistically associated with an increased probability of lethal outcome or admission to the ICU.

Table 1. Patients' demographic and clinical characteristics

Variables		n (%)
Sex	Male	7 (58.3)
	Female	5 (41.7)
Mean age in years ± SD		61.54 ± 10.37
Comorbidities		
Hypertension		9 (30)
Diabetes mellitus		3 (10)
Myocardial infarction		2 (6.6)
Chronic pulmonary disease		1 (3.3)
Autoimmune diseases		2 (6.6)
Malignancy		2 (6.6)
Chronic kidney disease		5 (16.6)
Other		6 (20)
With acute respiratory distress		7 (58.3)
With secondary bacterial infection		7 (58.3)
Multiple organ support		
NIV		1 (8.3)
HFNC/NIV		1 (8.3)
MV and vasopressor support with norepinephrine		7 (35.8)
Supplemental oxygen		2 (16.7)
Extracorporeal membrane oxygenation		1 (8.3)
SAPS II/MEWS score 24 hours before CRRT		
SAPS II		7 (58.3)
SAPS II score (Mean ± SD)		39 ± 5.92
MEWS score		
1		3 (60)
3		2 (40)
Anuric patients 24h before CRRT		5 (41.7)
Start of CRRT from admission (days) (Mean ± SD)		9.17 ± 7.16
Padua Prediction Score for Risk of VTE		
< 4		3 (25)
≥ 4		9 (75)
Therapy		
Antibiotics		9 (20.9)
Hemomycin		12 (27.9)
Chloroquine		3 (6.9)
Antivirals		2 (4.6)
Corticosteroids		12 (27.9)
Intravenous immunoglobulins		2 (4.6)
Antifungal		3 (6.9)
Dose of Thrombophylaxis (IU)		
dalteparin-sodium 2500 IU/12h		11 (91.6)
dalteparin-sodium from 2500 IU to 10000 IU/12h		1 (8.3)
Nonsurvivors		9 (75)
Length of hospital stay (Mean ± SD)		14.92 ± 10.90

CRRT – continuous renal replacement therapy; HFNC – high-flow nasal cannula; SAPS II – simplified acute physiology score; MEWS – modified early warning score; MV – invasive mechanical ventilation; NIV – noninvasive ventilation; VTE – venous thromboembolism

The criteria for initiating CRRT according to Kidney Disease Improving Global Outcomes were the stages 2 or 3 AKI.

CRRT was performed on two devices each having its own filter: Multifilter (high-flux filter Kit8 CVVHDF 1000,

Table 2. Comparison of laboratory values between patients before and after CRRT

Variables	Before CRRT (IQR)	After CRRT (IQR)	p
Leukocytes ($10^9mm^3/l$)	12.9 (6.9–21.1)	18.3 (6.7–34.2)	**0.041***
Lymphocytes (%)	7.5 (6.4–11.8)	6.3 (2.5–11.4)	0.158
Hemoglobin (g/L)	84.5 (75.5–95.8)	88.0 (72.5–107)	0.475
Platelets ($10^9mm^3/l$)	191.0 (114.7–267)	170.5 (84.7–207.2)	0.065
CRP (mg/l)	178.9 (40.1–289.3)	176.2 (32.8–344.8)	0.859
PCT (ng/l)	2.1 (1.2–9.3)	1.45 (0.59–4.14)	0.346
Urea (mmol)	26.5 (21.1–36.3)	16.9 (9.3–23.3)	**0.005***
Creatinine (μmol)	486.0 (257.2–804)	308.0 (156.2–604.7)	**0.002***
Potassium (mmol)	4.9 (4.1–5.3)	4.3 (3.9–4.8)	**0.049***
Sodium (mmol/l)	144.0 (138.5–147)	139.0 (137.2–141.7)	0.065
Chlorine (mmol	106.0 (105–108.7)	102.5 (101–104)	**0.008***
Magnesium (mmol)	1.01 (0.79–1.07)	0.84 (0.76–0.97)	**0.021***
AST (U/L)	40.0 (35–104.5)	68.0 (43.7–110.2)	**0.003***
ALT (U/L)	42.0 (28.7–67)	74.0 (44.2–92.2)	**0.002***
GGT (U/L)	94.5 (43.2–115.7)	109.5 (73.7–141.2)	**0.002***
APTT (R)	1.33 (1.12–1.70)	2.96 (1.69–73.9)	**0.005***
PT (R)	1.15 (1.08–1.24)	1.43 (1.15–1.90)	**0.011***
Fibrinogen (g/L)	4.2 (2.40–5.27)	3.5 (2.37–5.25)	0.326
D-dimer (mg/L)	1680 (869.5–4373.2)	2278.5 (1075–5460.7)	0.182

CRRT – continuous renal replacement therapy; IQR – interquartile range; aPTT – activated partial thromboplastin time; PT – prothrombin time; R – ratio; ALT – alanine aminotransferase; AST – aspartate aminotransferase, GGT – gamma-glutamyl transferase; CRP – C-reactive protein; PCT – procalcitonin; aPTT – activated partial thromboplastin time; PT – prothrombin time; *p < 0.05 (*Wilcoxon test based on negative and positive ranks*)

Bad Homburg, Germany) and Prismaflex (high-flux filter ST150 Gambro, Deerfield, IL, USA). EMiC2 Hemofilter (Fresenius Medical Care, Bad Homburg, Germany, 1.8 m^2 surface area) and oXiris (Gambro, AN-69 based membrane, surface treated by polyethyleneimine and grafted with heparin) were administered in septic patients.

Statistical analysis

Descriptive and inferential statistical methods were used for the data analysis. Numerical characteristics are presented by the arithmetic mean, the median with interquartile range (IQR 25–75%) and the standard deviation, while the attributive characteristics are expressed by frequency and percentage. Given the sample size, i.e., the small number of frequencies to compare differences between the groups, the Wilcoxon test for paired samples was used, an alternative to the Student's t-test for two dependent samples. There was a statistical significance if $p < 0.05$, and a high statistical significance if $p < 0.001$. The IBM SPSS Statistical Package for Social Sciences 21 software package was used for statistical data processing.

RESULTS

The study included 12 COVID-19 patients with AKI (58.3% men), with a mean age of 61.54 ± 10.37 years of age. The most common comorbidity was hypertension in nine patients.

ARDS with secondary bacterial infection was found in seven (58.3%) patients who required MV and CRRT. Before CRRT, the average values of the SAPS II score were 39 ± 5.92 in 58.3% severely ill patients, while five of them (41.7%) were anuric. The average time for the start of CRRT from admission to the hospital was 9.17 ± 7.16 days. Nine patients had Padua Prediction Score for Risk of VTE ≥ 4. Median hospitalization time was 14.92 ± 10.90 days, mortality was 75%. The doses of thromboprophylaxis and the type of therapy used are also shown Table 1.

Table 2 shows the comparison in laboratory parameters before and after CRRT. Leucocyte count, hepatogram (AST, ALT, GGT), aPTT, and PT increased significantly after CRRT, in contrast to the levels of urea, creatinine, potassium, chloride and magnesium, which decreased, as expected.

The total of 20 CRRT procedures and six CRRT + extracorporeal membrane oxygenation (ECMO) were done, and the average number of procedures was 2.16 per patient. The most common modality was pre-dilution continuous veno-venous hemodiafiltration (CVVHDF) and the most commonly used membrane was highly adsorptive-oXiris membrane. The average duration of procedures in 11 patients was 24.8 h, with the CVVHDF + ECMO procedure performed in one patient lasting a total of 315.5 h. The median value of dialysate flow was 1558.3 ml/h, and median value of replacement flow was 1318.1 ml/h. The average CRRT dose in nine septic patients was 36.6 ml/kg/h and in the remaining patients 30 ml/kg/h. The average ultrafiltration per procedure in 11 patients was 4736.4 ml, while the total ultrafiltration in a patient who underwent CVVHDF and ECMO was 15.669 ml. The average bolus dose was 3250 ± 1138.18 IU while the continuous UFH dose was 1112.5 ± 334.48 IU/kg/h. The continuous dose of UFH during CRRT was increased by 1/3 in six patients (66.7%), while it was increased by 1/2 in (33.3%) patients. Discontinuation of CRRT was necessary in three patents (25%) – in the first case due to the clotting circuit, in the second case for technical reasons and in the third case due the hemodynamic instability and the fall of oxygen saturation. Table 3.

DISCUSSION

In addition to hemostatic disorders, immobility, and systemic inflammation, MV and central venous catheters contribute to the risk of VTE in ICU. Dietary deficiencies and liver dysfunction can also interfere with the synthesis of coagulation factors. Due to organ dysfunction, critically ill patients develop changes in pharmacokinetics, which may require adjustment of the anticoagulant dose [15]. Our patients had different levels of D-dimer depending on the severity of their clinical conditions as well as secondary infections. They had minor disorders of the hemostasis mechanism without developing of disseminated intravascular coagulation were verified, which corresponds to the results of a Dutch study [16]. Using the Padova Predic-

Table 3. Treatment parameters of CRRT

Variables	n (%)
Number of procedures CRRT	
1	5 (41.7)
2	4 (33.3)
3 or more	3 (25)
Types of CRRT modalities	
Predilution CVVHDF	8 (66.7)
Predilution CVVHDF + ECMO	1 (8.3)
CVVH	1 (8.3)
CVVHD	3 (25)
Type of adsorptive membrane	
EMIC2	2 (16.7)
OXIRIS	7 (58.3)
Kit 8	2 (16.7)
ST 150	1 (8.3)
Dose of CRRT	
≥ 35 ml/min/h	9 (75)
< 35 ml/min/h	3 (25)
Bolus dose of UFH (IU) (Mean±SD)	3250 ± 1138.18
Continuous dose of UFH (IJ/kg/h) (Mean±SD)	1112.5 ± 334.48
Increasing the continuous dose of UFH during CRRT	
1/3	6 (66.7)
1/2	3 (33.3)
Interruption of the CRRT	
Yes	3 (25)

CRRT – continuous renal replacement therapy; ECMO – extracorporeal membrane oxygenation; CVVHDF – continuous venovenous hemodiafiltration; CVVH – continuous venovenous hemofiltration; CVVHD – continuous venovenous hemodialysis; UFH – unfractionated heparin

tion Score for Risk of VTE, the risk ≥ 4 was determined in 75%, i.e., nine patients, (seven critically ill patients and two treated in semi-intensive care). Unlike other published studies, no patient developed a thrombotic event [16, 17, 18]. Namely, the authors of the Dutch study reported that 31% out of 184 COVID-19 patients had arterial and venous thrombotic events, although all patients had standard thromboprophylaxis [16]. The authors of another study also used the Padova score and showed that 40% of the patients were at risk for VTE, although the study did not provide the data on the use of VTE prophylaxis or an incident with VTE [18]. In two French ICUs, the overall rate of VTE in patients was shown to be very high at 69%, but only 31% of them were treated with prophylactic anticoagulation [17].

Our patients were at risk for developing AKI due to the presence of the most common comorbidities such as hypertension, chronic renal failure, diabetes and heart disease, use of diuretics and ACE inhibitors, which corresponds to the published results of other authors [19]. The onset of some CRRT methods was individually assessed based on clinical and laboratory parameters, in accordance with the current guidelines. Compared with traditional CRRT indicators in patients with an onset of AKI, the leading criterion was hypervolemia for the purpose of respiratory support. All patients had a double-lumen catheter placed in the right internal jugular vein, in accordance with the recommendations [20].

Depending on the availability of modalities, supply of dialysis material, adsorption membranes and cytosorber, the recommendation for critically ill patients is CVVH or CVVHDF targeting minimum delivery dose of 20–25 mL/kg/h [21]. In the study period, in COVID-19 confirmed patients requiring dialysis procedures, we were able to organize only the implementation of CRRT with heparin anticoagulation, with a predominance of pre-dilution CVVHDF and highly adsorbent membranes (oXiris, EMiC2) in nine (75%) patients with high proinflammatory parameters. In these patients CRRT dose was 35–40 mL/kg/h in order to eliminate inflammatory mediators, while other patients where the main goal was volume maintenance had CRRT 25–30 mL/kg/h. During the procedures, the doses of antibiotics were adjusted and the energy needs increased by 20–30 (kcal/kg.d), protein 1.5 ≤ 1.7 (g kg.d) and amino acids 1.5 ≤ 1.7 (g kg.d) according to the individual treatment regimen [22].

So far, papers on premature filter coagulation have been published frequently. In a multicenter French cohort of 150 patients, 29 of them were treated for RRT and 28 of them (97%) experienced a thrombosis circuit, with a shortened lifetime of the circuit [9]. The anticoagulation of the circuit has not been specifically analyzed, however, all the patients received at least thromboprophylaxis, and 30% of them had therapeutic doses of heparin. In a further study in one center with 69 critically ill patients with COVID-19, nine out of 11 patients had increased therapeutic UFH infusions due to thrombosis of recurrent circuits [23]. A third unicenter study reported filter coagulation in eight out of 12 severely ill patients with COVID-19 on hemofiltration, despite anticoagulation with prophylactic doses. Out of the four patients without filter clotting, three were on therapeutic UFH infusion due to existing thrombosis at the time of the hemofiltration onset [24].

The optimal anticoagulant strategy to prevent circuit coagulation and ensure CRRT efficacy is unknown in COVID-19. Since 75% of our patients had the Padua score ≥ 4, in order to prolong the filter life, pre-dilution CVVHDF with antithrombotic oXiris membrane was applied in 58.3% of critically ill patients with high inflammatory parameters and D-dimer. Wen et al. [25] have not determined the correlation between D-dimer values and shortened sustained low-efficiency dialysis sessions in around 30% patients, in contrast with the study done by Valle et al. [26], who proved that the higher levels of D-dimer indicate a higher rate of filter coagulation in CRRT in 46.6% patients. However, the results are not comparable due to the lower values of D-dimer, different treatment modalities and the lack of details on coagulation in the first study. Also, neither study monitored Anti-Xa and determined antithrombin III and the factor VIII. The correlation of higher values of CRP with shorter sustained low-efficiency dialysis duration was determined in the first study, which indicates the correlation between hyper-inflammation in COVID-19 patients and the coagulation of extracorporeal circuit. Elevated CRP levels in the acute phase are related to hyper viscosity, and the latter was diagnosed in severely ill COVID-19 patients [27, 28]. Our study did not analyze the

correlation between D-dimer and CRP with filter coagulation due to the proportion of the samples, and the fact that only one patient had clotting circuit.

The recommended start dose of UFH is 10–15 IU/kg per hour and the aPTT is 60–90 seconds [21]. In our study, in six patients (50%) the values of hemostasis parameters and platelets allowed the initial increase by 1/3 to 1/2 of the recommended bolus dose of UFH, and we increased the UFH dose until we reached the target values of aPPT ranging 180–220 seconds. Despite the administration of higher bolus doses of UHF, during CRRT all six patients required a dose increase, as well as the two patients (with malignant disease) treated in surgical intensive care unit in whom an adsorptive EMiC2 membrane was used. In case of using ECMO + CRRT blood flow was maintained at > 400 ml/min [29]. The patient who underwent ECMO + CVVHDF was prescribed UFH according to the guidelines of non-COVID-19 patients [30].

No bleeding, no heparin resistance, and no heparin-induced thrombocytopenia were found in any of the patients. However, CRRT was discontinued in one patient due to circuit clotting, therefore, the dose was increased to the upper limit of thromboprophylaxis to prevent recurrent circuit clots.

Until we obtain more precise recommendations on the amount of bolus and continuous doses of UFH for COVID-19 patients, one should take into consideration comorbidities, the doses of thromboprophylaxis, the type of RRT modalities and highly adsorptive membranes, the planned duration of the procedure and the level of ultrafiltration.

During the earliest period of the pandemic, two patients were treated with antiviral drugs (Lopinavir/Ritonavir), both of them took azythromicin and corticosteroids in the recommended doses [5]. Hydroxychloroquine was introduced in three patients. It is known that this drug can have an antithrombotic effect, especially on antiphospholipid antibodies, which we were not able to analyze during the epidemic. Two patients used antiplatelet and anticoagulant therapy for acute coronary syndrome and atrial fibrillation prior to COVID-19.

The average duration of hospitalization of our patients who required CRRT was 14.92 ± 10.90 days, similar to some published data [31]. The mortality was 75%, while in the studies done it ranges between od 63.3–90% [32, 33, 34].

There are some limitations associated with our study. This is a single-center study, covering a small number of patients during a short period of time. All our patients were treated with CRRT, there was no control group due to limited data availability, and we have no insight into the incidence of AKI in patients treated with conservative treatment.

CONCLUSION

Implementation of pre-dilution CVVHDF with antithrombin membrane and the UFH doses higher by 1/3 to 1/2 than the recommended ones, has extended the filter life without complications in our COVID-19 patients with high inflammatory parameters and D-dimer and an estimated risk of developing deep vein thrombosis. The need for a unified strategy in the diagnosis and optimization of AKI treatment with a better understanding of COVID-19 would contribute to determining the optimal approach to CRRT in these patients.

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Значај антикоагулације при континуираној замени функције бубрега код болесника са акутним оштећењем бубрега повезаним са ковидом 19

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САЖЕТАК

Увод/Циљ У Србији је пандемија вирусне болести корона 2019 (ковид 19) почела почетком марта 2020. године. Циљ овог рада је сумирање клиничког искуства у лечењу акутног оштећења бубрега повезаног са ковидом 19 методама континуиране замене функције бубрега (КЗФБ) са фокусом на висини примењене дозе нефракционисаног хепарина.

Методе Приказаћемо 12 болесника лечених КЗФБ-ом на Клиници за инфективне болести у Клиничком центру Војводине од 6. марта до 20. маја 2020. године. Анализирани су антитромботска профилакса, ризик од венске тромбоемболије, примењена терапија, биохемијски параметри пре и после КЗФБ-а, антикоагулација и други параметри КЗФБ-а.

Резултати Просечна старост болесника је била 61,54 ± 10,37 година и седам болесника (58,3%) било је мушког пола. Сви су примали стандардну тромбопрофилаксу. Падуа скор предикције ризика од венске тромбоемболије ≥ 4 имало је девет (75%) болесника, али ниједан није развио тромботски догађај. Акутно оштећење бубрега зависно од дијализе развило је седморо критично оболелих са мултиорганском дисфункцијом. Просечна доза КЗФБ-а је износила 36,6 *ml/kg/h*, просечна болусна доза нефракционисаног хепарина била је 3250 ± 1138,18 *IJ*, а континуирана доза 1112,5 ± 334,48 *IJ/kg/h*. Прекид КЗФБ-а због коагулације сета био је неопходан само код једног болесника. Вредности леукоцита, *AST*, *ALT*, *GGT*, *aPTT* и *PT* биле су значајно веће после КЗФБ-а у поређењу са уреом, креатинином, калијумом, хлором и магнезијумом, чије су вредности биле значајно мање.

Закључак Код наших болесника оболелих од ковида 19 са високим инфламаторним параметрима и Д-димером, као и процењеним ризиком од развоја тромбозе дубоких вена, примена предилуционе континуиране веновенске хемодијафилтрације са антитромботском мембраном и вишим дозама за ⅓ до ½ нефракционисаног хепарина у односу на препоручене дозе, омогућила је дужи век трајања филтера, без појаве компликација.

Кључне речи: вирусна болест корона 19; континуирана замена функције бубрега; акутно оштећење бубрега; тромботски догађаји