ANTIKOAGULANSI I KORTIKOSTEROIDI U LEČENJU KOVID-19 OBOLJENJA – ŠTA ZNAMO DO SADA?

ANTICOAGULANTS AND CORTICOSTEROIDS IN COVID-19 – WHAT DO WE KNOW SO FAR?

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SAŽETAK

Više od godinu i po dana traje borba protiv pandemije KOVID-19 oboljenja. Kao nezaobilazni deo najnovijih protokola, razmatra se upotreba kortikosteroida i antikoagulanasa u lečenju, ali i u prevenciji komplikacija. Na ovom mestu, želimo da prikažemo prednosti, ali i mane, upotrebe kortikosteroidne i antikoagulantne terapije u infekciji Sars-KoV-2 virusom, u skladu sa dostupnim podacima.

Na samom početku pandemije, uočena je veća učestalost trombotičkih događaja koji pogoršavaju tok i ishod oboljenja. Pokazalo se da povišene vrednosti D-dimera ne koreliraju sa postojanjem venske tromboze i nisu pouzdan dokaz duboke venske tromboze ili plućne tromboembolije. Prema Nacionalnom protokolu za lečenje obolelih od KOVID-19 infekcije (12. verzija), preporučuje se upotreba antikoagulantne terapije kod hospitalizovanih bolesnika. S obzirom na postojanje rizika od nastanka različitih neželjenih reakcija, poput krvarenja i heparinom uzrokovane trombocitopenije, potrebno je pažljivo ordiniranje antikoagulantne terapije, uz praćenje njenih efekata.

Kada su u pitanju kortikosteroidi, naglasak je na njihovoj efikasnosti kod pacijenata sa umereno teškom i teškom kliničkom slikom koji zahtevaju kiseoničku potporu. Efikasnost kortikosteroidne terapije se ogleda u snižavanju mortaliteta, smanjenju potreba za mehaničkom ventilacijom i bržim prevođenjem obolelih iz jedinica intenzivnog lečenja, kao i kraćem trajanju hospitalizacije.

Individualna procena koristi i rizika pri uključivanju ovih lekova u terapiju bolesnika sa potvrđenom infekcijom Sars-KoV-2 virusom je od vitalnog značaja za postizanje željenih efekata terapije.

Ključne reči: KOVID-19, SARS-KoV-2, antikoagulantna terapija, tromboza, kortikosteroidi

ABSTRACT

It has been a year and a half since the fight against the COVID-19 pandemic started. In today's protocols for the treatment of COVID-19 and the prevention of its complications, corticosteroid therapy and anticoagulant therapy have a crucial part. The goal of this article is to show, based on available data, both the benefits and the disadvantages of corticosteroid and anticoagulant therapy in treating the infection caused by the Sars-CoV-2 virus.

At the very onset of the pandemic, an increased frequency of thrombotic events negatively impacting the course and outcome of the disease, was registered. It has been observed that increased values of D-dimer in patients with COVID-19 do not correlate with the presence of venous thrombosis and are not reliable in the detection of deep vein thrombosis and pulmonary thromboembolism. According to the National Protocol for Treating COVID-19 (Version 12), anticoagulant therapy is recommended in hospitalized patients. Due to the risk of different side effects, such as bleeding and heparin-induced thrombocytopenia, a careful use of anticoagulant therapy is necessary, as well as close monitoring of its effects.

With respect to corticosteroids, their efficacy in patients with moderate and severe clinical presentation of COVID-19, who are in need of oxygen support, was analyzed. Corticosteroids have proven efficient in decreasing mortality, decreasing the need for mechanical ventilation, decreasing the length of stay in intensive care units, as well as in shortening the length of hospital stay.

Assessing the individual benefits and risks before introducing these drugs into the therapy of a patient with confirmed COVID-19 is of vital importance for achieving the desired effects of the therapy.

Keywords: COVID-19, SARS-CoV-2, anticoagulants, thrombosis, corticosteroids.

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UVOD

Decembra 2019. godine, u Vuhanu (Kina), javili su se prvi slučajevi atipične pneumonije izazvane SARS-KoV-2 virusom (engl. *severe acute respiratory syndrome coronavirus 2 – SARS-CoV-2*) [1]. Odatle se bolest veoma brzo proširila po celom svetu, i 11. marta 2020. godine, Svetska Zdravstvena Organizacija je proglasila pandemiju [2]. Od tada traje borba protiv pandemije KOVID-19 oboljenja (engl. *coronavirus disease 2019*). Pored svih napora na globalnom nivou, ona je i dalje u punom jeku.

Pacijenti koji boluju od ove nove infektivne bolesti od simptoma najčešće prijavljuju povišenu telesnu temperaturu, suv kašalj, zamor, osećaj kratkog daha (dispneja), a ređe glavobolju, hemoptiziju i proliv. Gubitak osećaja mirisa (anosmija) i ukusa (ageuzija) takođe su prisutni [3,4].

Do početka decembra 2021. godine, u svetu je registrovano više od 251.000.000 obolelih i preko pet miliona umrlih. Za isto vreme, u Srbiji je bilo preko milion obolelih i preko jedanaest hiljada umrlih [5].

Na početku pandemije, činilo se da ova infekcija zahvata samo disajne organe, međutim kako je vreme proticalo, otkrivene su različite manifestacije koje se mogu javiti i na nervnom, kardiovaskularnom, gastrointenstinalnom, bubrežnom, endokrinom, mišićnom, krvnom, odnosno, na svim sistemima [6].

Trenutno ne postoji specifičan lek protiv ove bolesti, a terapijski protokoli razlikuju se unekoliko od države do države. U Srbiji se, danas, lečenje sprovodi po dvanaestoj reviziji Terapijskog protokola [7]. Protokoli za lečenje počeli su da se prave od februara 2020. godine, i menjali su se shodno novim saznanjima i iskustvima iz svih zahvaćenih područja. Kao nezaobilazni deo aktuelnih protokola, razmatra se upotreba kortikosteroida i antikoagulanasa, ali i prevencija njihovih komplikacija. Bez obzira na do sada prikupljene dokaze o njihovoj dobrobiti, još uvek postoje nesuglasice u vezi sa preciznim indikacijama i kontraindikacijama za primenu i doziranje ovih lekova.

Antikoagulantna terapija se odavno koristi u terapiji širokog spektra bolesti i patoloških stanja [8]. Ovaj terapijski modalitet se svakodnevno razvija otkrićem oralnih antikoagulantnih lekova, koji su se pridružili postojećim intravenskim i subkutanim preparatima, čime su povećane terapijske mogućnosti tromboprofilakse i antikoagulacije. S obzirom na farmakokinetske i farmakodinamske razlike među različitim lekovima, potreban je individualni pristup koji će osigurati optimalni terapijski ishod [9].

Zbog njihovog antiinflamatornog, ali i imunosupresivnog dejstva, upotreba kortikosteroida u lečenju KOVID-19 oboljenja predstavlja predmet stručnog razmatranja kliničara širom sveta [10,11].

INTRODUCTION

The first cases of atypical pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were registered in December 2019, in Wuhan (China) [1]. The disease very quickly spread all over the world and, on March 11, 2020, the World Health Organization declared the coronavirus disease 2019 (COVID-19) pandemic [2]. The fight against the pandemic has been ongoing ever since. Despite all of the efforts made at the global level, the pandemic is still in full swing.

Patients suffering from this new infectious disease most commonly report the following symptoms: elevated body temperature, dry cough, fatigue, shortness of breath (dyspnea), and, less frequently, headache, haemoptysis, and diarrhea. Loss of the sense of smell (anosmia) and loss of the sense of taste (ageusia) also occur [3,4].

Until the beginning of December 2021, more than 251.000.000 COVID-19 patients and more than five million COVID-19 related deaths were registered worldwide. During the same period, in Serbia, there were more than a million COVID-19 cases and more than eleven thousand COVID-19 related deaths [5].

At the beginning of the pandemic, it seemed that the infection was limited to the respiratory organs, however, as time elapsed, different manifestations of the disease were discovered, occurring at the level of the nervous, cardiovascular, gastrointestinal, renal, endocrine, muscular, sanguineous, i.e., within all body systems [6].

At present, there is no specific drug for this disease, and the treatment protocols vary, somewhat, from country to country. In Serbia, at present, treatment is carried out according to Version 12 of the National Protocol for Treating COVID-19 [7]. The development of treatment protocols started as of February 2020, and they have been changing over time, in keeping with new knowledge and experience coming from all regions of the world affected by COVID-19. An essential part of all current protocols is considering the introduction of corticosteroids and anticoagulants, but also preventing potential complications caused by the use of these drugs. Regardless of the evidence gathered so far on the benefits of their use, there is still an ongoing debate regarding the precise indications and contraindications in the application and dosing of these drugs.

Anticoagulant therapy has long been in use for the treatment of a wide range of diseases and pathological states [8]. This treatment modality is constantly being developed further with the advent of oral anticoagulants, which have now been added to the range of possible treatment, alongside existing intravenous and subcutaneous drugs, thus widening treatment options for thromboprophylaxis and anticoagulant therapy.

S obzirom da, pored koristi, upotreba ovih lekova može imati i neželjena dejstva, potrebno je jasno definisanje indikacija i kontraindikacija za njihovu upotrebu. U više zemalja sveta sprovedene su različito osmišljene studije sa jednim istim ciljem, a to je da se proceni uticaj kortikosteroida na tok bolesti kod pacijenata sa KOVID-19 infekcijom. Rezultate svih ovih studija objedinila je Svetska zdravstvena organizacija u Šestom protokolu, objavljenom 24. septembra 2021. godine [12].

KOVID-19 I TROMBOZA

U populaciji pacijenata obolelih od oboljenja KOVID-19, uočeni su različiti poremećaji pomoću skrining testova i specifičnih testova hemostaze. Posebnu pažnju privukle su povišene vrednosti D-dimera, koje koreliraju sa stepenom težine oboljenja [13]. U brojnim studijama, D-dimer je prikazan kao nezavisni prediktor smrtnog ishoda u toku bolničkog lečenja [14-16].

Tromboze predstavljaju značajne komplikacije KOVID-19 oboljenja, koje u mnogome pogoršavaju tok i ishod bolesti. Već na početku pandemije viđene su veće učestalosti trombotičkih događaja. Kod bolesnika koji su lečeni u jedinicama intenzivnog lečenja (JIL), duboka venska tromboza zabeležena je kod 25% pacijenata, kao i tromboembolija pluća [18]. Uprkos sistematskoj antikoagulantnoj profilaksi, kod 31% kritično obolelih pacijenata se razvija tromboza (venska i arterijska) [19].

U metaanalizi, koja je uključila 1.599 kritično obolelih pacijenata, učestalost venskog tromboembolizma je bila 28,4%, učestalost tromboze dubokih vena (TDV) je bila 25,6%, a učestalost plućne embolije je iznosila 16,4%. Veća učestalost TDV-a viđena je u studijama rutinske analize svih bolesnika nego što je uočena u studijama gde su evaluirani bolesnici sa kliničkom sumnjom na TDV. Tome u prilog govore i rezultati metaanalize, koja je obuhvatila 91 studiju i ukupno 35.017 bolesnika, a koja zaključuje da je učestalost venske tromboze kod bolesnika lečenih u jedinicama intenzivnog lečenja 24,1%, nasuprot 7,7% lečenih izvan JIL-a. Učestalost trombotičkih komplikacija kod dece je niska i iznosi 0,7%, tačnije od 537 SARS-KoV-2 pozitivne dece (medijana godina: 61 mesec, IQR: 6 – 140) njih četvoro je razvilo vensku trombozu (od ukupnog broja, 68,5% je bilo hospitalizovano, a 10,8% je zahtevalo lečenje u JIL-u) [20,21].

U metaanalizi, koja je uključila 41.768 bolesnika, ispitivan je relativni rizik za razvoj tromboze kod bolesnika sa KOVID-19 oboljenjem i kod obolelih od drugih bolesti slične težine (grip, ARDS prouzrokovan nekim drugim uzrokom, vanbolničke pneumonije). U ovoj studiji nije uočen veći rizik za pojavu tromboze kod KOVID-19

Bearing in mind the pharmacokinetic and pharmacodynamic differences among the different drugs, an individualized approach is necessary in order to ensure and optimal treatment outcome [9].

Due to their anti-inflammatory, but also their immunosuppressive effects, the use of corticosteroids in the treatment of COVID-19 is being analyzed and assessed by clinicians all over the world [10,11].

Bearing in mind that, in addition to benefits, the use of these drugs may also have adverse effects, it is necessary to have clearly defined indications and contraindications for their application. Differently designed studies have been carried out in a number of countries of the world, with the same goal – to assess the impact of corticosteroids on the course of the disease in patients with COVID-19. The results of these studies have been aggregated by the World Health Organization within the Sixth Protocol, published on September 24, 2021 [12].

COVID-19 AND THROMBOSIS

In the population of patients suffering from COVID-19, different disorders have been discovered with the help of hemostatic screening tests and specific hemostasis tests. Elevated levels of D-dimer, which correlate with the degree of severity of the disease, have especially drawn the attention of researchers and clinicians [13]. D-dimer has been reported as an independent predictor of mortality during in-hospital treatment, in a number of studies [14-16].

Thromboses are significant complications of COVID-19 as they have a considerably negative impact on the course and outcome of the disease. At the very onset of the pandemic, higher frequencies of thrombotic events were registered. In patients treated in intensive care units (ICU), deep vein thrombosis was registered in 25% of patients, as well as pulmonary thromboembolism [18]. Despite systematic anticoagulant prophylaxis, thrombosis (venous or arterial) develops in 31% of critically ill patients [19].

In a meta-analysis involving 1,599 critically ill patients, the frequency of venous thromboembolism was 28.4%, the frequency of deep vein thrombosis (DVT) was 25.6%, while the frequency of pulmonary embolism was 16.4%. A higher frequency of DVT was registered in studies including routine analysis of all patients than in studies where only patients with clinically suspected DVT were evaluated. The results of a meta-analysis involving 91 studies with a total of 35,017 patients speak also to that effect. The conclusion of that study is that the frequency of venous thrombosis in patients treated in ICUs is 24.1%, as opposed to 7.7% in patients treated outside ICUs. The frequency of thrombotic complications in children is low and amounts to

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oboljenja. Značajno veći rizik za pojavu tromboze je zabeležen kod obolelih od KOVID-19 infekcije lečenih u JIL-u [22]. Slične rezultate pokazala je druga studija koje je obuhvatila više od milion bolesnika [23].

Po svemu sudeći, može se zaključiti da venska tromboza kod bolesnika pozitivnih na SARS-KoV-2 virus pokazuje veliku učestalost, pogotovo kod bolesnika koji zahtevaju lečenje u JIL-u, kao i da venska tromboza zahteva posebnu pažnju u pogledu prevencije, ranog otkrivanja i lečenja.

Učestalost trombotičkih komplikacija ukazuje na to da se najverovatnije radi o više različitih molekularnih interakcija između virusa i organizma, koje dovode do ove neželjene posledice. U ljudskom organizmu, SARS-KoV-2 virus vezuje se za angiotenzin-konvertujući enzim 2 (engl. *angiotensin-converting enzyme 2 – ACE2*), koji prevodi angiotenzin II u angiotenzin 1-7, što posledično dovodi do povećanja nivoa angiotenzina II (koji ima proinflamatorne i protrombotičke efekte) u krvi. S druge strane, usled smanjenja nivoa angiotenzina 1-7, izostaju pozitivni antiinflamatorni i antitrombotički efekti ovog peptida. Pored ovoga, angiotenzin II je i moćan medijator oksidativnog stresa, što dovodi do nastanka reaktivnih oblika kiseonika, dok angiotenzin 1-7 ima suprotna, antioksidativna svojstva, indukcijom sinteze i oslobađanja azot-monoksida iz endotelnih ćelija. Sumirano, ova dva svojstva – povećanje reaktivnih oblika kiseonika i smanjenje azot-monoksida, štetno deluju na endotel. Pored navedenih posledica disregulacije renin-angiotenzin-aldosteron sistema na endotel, takođe dolazi i do povećane ekspresije LOX-1, COX-2, VEGF. Različitim istraživanjima pokazana je snažna veza između disfunkcionalnog endotela i nastanka tromboze. Endotelna disfunkcija dovodi do aktivacije različitih mehanizama koagulacije, a ona je takođe povezana i sa povećanom ekspresijom pojedinih protrombotičkih molekula na površini ćelija [24,25].

Potencijalni način stimulacije agregacije trombocita i tromboze je oslobađanje von Vilebrandovog faktora iz subendotelnih prostora usled disfunkcije endotela i njegovog oštećenja, zbog čega dolazi do njegove polimerizacije i aktivacije [26].

Pored svega navedenog, do tromboze kod KOVID-19 oboljenja potencijalno može doći i zbog poremećaja imunog sistema. Citokinska oluja, za koju se zna da se javlja u okviru ove bolesti, dovodi do disregulacije koagulacionog sistema usled aktivacije različitih imunih koagulacionih kaskada, što posledično dovodi do zgrušavanja krvi [27-29].

D-dimer se koristi rutinski u kliničkoj praksi, kod sumnje na duboku vensku trombozu i plućnu emboliju, u kojim stanjima dostiže visoke vrednosti, pa merenje ovog markera ima senzitivnost iznad 95% [30].

0.7%, more precisely, out of 537 SARS-CoV-2 positive children (median age: 61 months, IQR: 6 – 140), four of them developed venous thrombosis (68.5% of the total number were hospitalized, while 10.8% required treatment in the ICU) [20,21].

In a meta-analysis involving 41,768 patients, the relative risk for thrombosis development was analyzed in COVID-19 patients and in patients suffering from other diseases of similar severity (the flu, ARDS resulting from causes other than COVID-19, out- of-hospital-pneumonia). In this study, an increased risk of thrombosis development was not registered in COVID-19. A significantly higher risk of thrombosis was registered in COVID-19 patients treated in ICUs [22]. Another study involving more than a million patients showed similar results [23].

Based on the above, one might conclude that venous thrombosis in SARS-CoV-2 positive patients has a high frequency, especially in patients requiring ICU treatment, as well as that venous thrombosis requires special attention in terms of prevention, early detection, and treatment.

The frequency of thrombotic complications indicates that, most probably, several different molecular interactions between the virus and the host body are at play, leading to this adverse effect. In the human body, the SARS-CoV-2 virus binds with angiotensin-converting enzyme 2 (ACE2), which converts angiotensin II into angiotensin 1-7, consequently leading to the increase in the level of angiotensin II (which has proinflammatory and prothrombotic effects) in the blood. On the other hand, due to the decrease in the level of angiotensin 1-7, positive anti-inflammatory and antithrombotic effects of this peptide are absent. Additionally, angiotensin II is a powerful mediator of oxidative stress, which leads to the formation of reactive forms of oxygen, while angiotensin 1-7 has opposing, antioxidative effects, through the induction of synthesis and the release of nitrogen monoxide from endothelial cells. The sum of these two – the increase in the reactive forms of oxygen and the decrease in the level of nitrogen monoxide, has a detrimental effect on the endothelium. In addition to the above stated consequences of the deregulation of the renin-angiotensin-aldosterone system on the endothelium, increased expression of LOX-1, COX-2, VEGF also occurs. Different studies have shown the existence of a powerful link between a dysfunctional endothelium and the development of thrombosis. Endothelial dysfunction leads to the activation of different coagulation mechanisms, and it is also linked to the increased expression of individual prothrombotic molecules on the cell surface [24,25].

The potential mode of the stimulation of thrombocyte aggregation and thrombosis is the release of the

Međutim, korišćenje D-dimera u dijagnostičke svrhe, radi detekcije tromboze, gubi značaj. Povišene vrednosti D-dimera kod bolesnika sa KOVID-19 infekcijom ne koreliraju sa postojanjem venske tromboze. Vrednosti D-dimera su povišene kao odgovor organizma na infekciju SARS-KoV-2 virusom, koji indukuje inflamaciju, te posledično dolazi do bronhoalveolarne hemostaze. Jedno od objašnjenja bilo bi da se, kao odgovor organizma na virus, stvaraju „zaštitni" mikrotrombovi, kako bi ograničili dalju invaziju i oštećenje. Razgradnja datih mikrotrombova je rezultat povišenih vrednosti D–dimera [30]. Upravo iz tih razloga, u ovom slučaju, vrednosti D-dimera nisu pouzdani parametar u detekciji duboke venske tromboze i plućne tromboembolije. Na vensku trombozu možemo posumnjati ukoliko se javi unilateralni otok ekstremiteta, te razvoj površinskog tromboflebitisa, a na emboliju pluća, ukoliko se pojavi dispneja ili pogoršanje hipoksemije, uprkos poboljšanja radioloških nalaza, kao i povećanje sistolnog pritiska u desnoj komori, uz porasta D-dimera (vrednosti iznad 5 mg/l; dvostruko veća vrednost u toku 24 h) [31].

ANTIKOAGULANTNA TERAPIJA U KOVID-19 INFEKCIJI

Prema Nacionalnom protokolu za lečenje obolelih od KOVID-19 infekcije (12. verzija), preporučuje se upotreba antikoagulantne terapije kod hospitalizovanih bolesnika. Standardne terapijske doze se ordiniraju bolesnicima koji imaju potrebu za lečenjem u JIL-u, dok se kod bolesnika lečenih na odeljenju, bolesnika sa suspektnom ili potvrđenom venskom trombozom, kao i kod pacijenata na dugotrajnoj antikoagulantnoj terapiji preporučuje upotreba terapijskih doza niskomolekularnog heparina (engl. *low-molecular-weight heparin – LMWH*) [7] (Tabela 1).

Na prvi pogled, zbunjujuće deluje primena terapijskih doza kod nekritičnih bolesnika, međutim, ova odluka pri izradi Nacionalnog protokola doneta je na osnovu multiplatformne randomizovane kontrolisane studije, koja je dokazala pozitivne efekte upotrebe terapijskih doza heparinskih preparata. Upotreba terapijskih doza smanjuje rizik od smrtnog ishoda u toku hospitalizacije, kao i rizik od neželjenih efekata kod respiratorne i kardiovaskularne potpore [32].

Međutim, primena terapijskih doza antikoagulantne terapije nije pokazala prednost kod kritično obolelih bolesnika pozitivnih na SARS-KoV-2 virus, lečenih u JIL-u, u odnosu na primenu profilaktičkih doza, u pogledu intrahospitalnog mortaliteta i dana bez kardiovaskularne i plućne podrške [33].

Primena antiagregacione terapije (acetilsalicilna kiselina) i antikoagulantne terapije ne preporučuje se kod bolesnika koji ne zahtevaju bolničko lečenje

Willebrand factor from subendothelial spaces, due to the dysfunction of the endothelium and its damage, which leads to its polymerization and activation [26].

In addition to all the above stated, thrombosis in COVID-19 can also potentially occur as the result of dysfunction within the immune system. The cytokine storm, which is known to occur within this disease, leads to the dysregulation of the coagulation system, due to the activation of different immune coagulation cascades, which consequently leads to the coagulation of blood [27-29].

D-dimer is routinely used in clinical practice when deep vein thrombosis and pulmonary embolism are suspected. In these conditions, D-dimer levels reach high values, which is why the measurement of this marker has a sensitivity above 95% [30]. However, using D-dimer for diagnostic purposes, i.e., detecting thrombosis, has been losing its significance. Elevated levels of D-dimer in COVID-19 patients do not correlate with the existence of venous thrombosis. D-dimer values are elevated as the body's response to infection with the SARS-CoV-2 virus, which induces inflammation, consequently leading to bronchoalveolar hemostasis. One of the explanations would be that 'protective' microthrombi are formed, as the body's response to the virus, in order to limit further invasion and damage. The degradation of these microthrombi is the result of elevated D-dimer levels [30]. It is for these reasons that, in this case, D-dimer levels are not a reliable parameter in the detection of deep vein thrombosis and pulmonary thromboembolism. Suspicion of venous thrombosis is warranted when unilateral swelling of an extremity occurs, as well as in case of the development of superficial thrombophlebitis, while pulmonary embolism may be suspected in the event of dyspnea, or if hypoxemia worsens despite improvement in radiological findings, as well as if there is an elevation in systolic pressure in the right ventricle with an increase of the D-dimer level (values above 5 mg/l; doubling of the value within 24 hours) [31].

ANTICOAGULANT THERAPY IN COVID-19

According to the National Protocol for Treating COVID-19 (Version 12), it is recommended that anticoagulant therapy should be used in hospitalized patients. Standard therapeutic doses are administered to patients who need to be treated in the ICU, while, in patients treated in hospital wards, in patients with suspected or confirmed venous thrombosis, as well as in patients on long-term anticoagulant therapy, the application of therapeutic doses of low-molecular-weight heparin (LMWH) is recommended [7] (Table 1).

At first glance, the application of therapeutic doses in noncritical patients seems confusing. However,

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Tabela 1. Preporuke za ordiniranje antikoagulantne terapije kod odraslih (na osnovu Nacionalnog protokola, 12. verzija) [7]

Gde se pacijent leči?	Koja antikoagulantna terapija se propisuje?	
U kućnim uslovima	Nije indikovana primena antikoagulantne i antiagregacione terapije.	
U bolnici	JIL	Profilaktičke doze LMWH-a
	Na odeljenju	Terapijske doze LMWH-a
	Pacijenti sa sumnjom ili potvrđenom venskom trombozom	Terapijske doze LMWH-a ili DOAK-a
	Pacijenti na dugotrajnoj antikoagulantnoj terapiji	Terapijske doze LMWH-a ili DOAK-a
Nakon otpusta iz bolnice	Ne preporučuje se tromboprofilaksa.*	

LMWH: engl. _low-molecular-weight heparin_ — heparin male molekularne težine (niskomolekularni heparin); DOAK: direktni oralni antikoagulanti — engl. _direct oral anticoagulants_

* Kod pacijenata koji daju anamnestički podatak o prethodnoj trombozi, o nedavnoj hirurškoj operaciji, značajnom smanjenju pokretljivosti, malignitetu i drugim trombogenim stanjima od značaja, može se razmotriti nastavak tromboprofilakse nakon otpusta iz bolnice.

Table 1. Recommendations for administering anticoagulant therapy in adults (based on the National Protocol, Version 12) [7]

Where is the patient treated?	Which anticoagulant therapy is prescribed?	
At home	Application of anticoagulant and antiaggregation therapy is not indicated.	
In hospital	ICU	Prophylactic doses of LMWH
	In hospital wards	Therapeutic doses of LMWH
	Patients with suspected or confirmed venous thrombosis	Therapeutic doses of LMWH or DOAC
	Patients on long-term anticoagulant therapy	Therapeutic doses of LMWH or DOAC
After discharge from hospital	Thromboprophylaxis is not recommended.*	

LMWH: low-molecular-weight heparin; DOAC: direct oral anticoagulants

* In patients who, in their anamnesis, provide data on previous thrombosis, a recent surgical procedure, significant decrease in mobility, malignancy, or other thrombogenic states that are of significance, the continuation of thromboprophylaxis after discharge from hospital may be considered.

KOVID-19 infekcije. Studija koja je ispitivala efekte četrdesetpetodnevne upotrebe antiagregacione i antikoagulantne terapije, došla je do zaključka da data terapija ne smanjuje rizik od pojave kardiovaskularnih i pulmonalnih komplikacija, u poređenju sa placebom, kod bolesnika koji ne zahtevaju bolničko lečenje [34].

Kao i pri propisivanju i upotrebi drugih lekova, treba biti obazriv pri korišćenju antikoagulantne terapije. Glavno neželjeno dejstvo je akutno krvarenje. Iako je relativno retko, ono može biti životno ugrožavajuće, te je neophodno da se ono blagovremeno prepozna i zaustavi [35]. U slučaju pojave manjeg krvarenja, mogu biti dovoljne lokalne hemostatske mere i revidiranje antikoagulantne terapije, a u slučaju pojave većeg i klinički značajnog krvarenja, treba obezbediti hemodinamsku potporu, transfuziju krvi i krvnih derivata, kao i hemostatsku potporu, te razmotriti ordiniranje adekvatnih antidota (poput upotrebe vitamina K kod antagonista vitamina K, protamin-sulfata kod heparina, itd.) [36]. Pored ovoga, pri upotrebi heparina može se javiti trombocitopenija izazvana heparinom (engl. _heparin-induced thrombocytopenia – HIT_). U pitanju je imunološka reakcija nakon upotrebe leka (najčešće nefrakcioniranog heparina, ili ređe heparina niske molekularne težine), koja dovodi organizam u protrombotičko stanje, a prepoznaje se po tome što dolazi do trombocitopenije u nekoliko dana od početka terapije heparinom i otkrivanja antitela na trombocitni faktor 4 [37,38]. HIT se može dovesti u vezu sa plućnom embolijom, ishemijskom nekrozom udova (koja zahteva amputaciju), akutnim infarktom miokarda, kao i moždanim udarom. Od najveće važnosti, u slučaju sumnje

when the National Protocol was being made, this decision was reached based on a multiplatform randomized controlled study, which has proven the positive effects of the use of therapeutic doses of heparin-based medication. The use of therapeutic doses reduces the risk of a lethal outcome during hospitalization, as well as the risk of adverse effects of respiratory and cardiovascular support [32].

However, the application of therapeutic doses of anticoagulant therapy did not demonstrate its advantage in critically ill SARS-CoV-2 positive patients treated in the ICU, as compared to the application of prophylactic doses, when it comes to intrahospital mortality and the number of days without cardiovascular or respiratory support [33].

The application of antiaggregation therapy (acetylsalicylic acid) and anticoagulant therapy is not recommended in COVID-19 patients who do not require in-hospital treatment. A study analyzing the effects of forty-five-day application of antiaggregation and anticoagulant therapy concluded that the said therapy did not reduce the risk of the occurrence of cardiovascular and pulmonary complications, as compared to the placebo, in patients not requiring in-hospital treatment [34].

As in prescribing and applying other medication, care should be taken in the application of anticoagulant therapy. The main adverse effect is acute bleeding. Although relatively rare, it can be life-threatening, which is why it is necessary that it should be recognized and stopped on time [35]. In case of minor bleeding, local hemostatic measures and anticoagulant therapy adjustment may be sufficient, and in case of major and clinically significant

na razvoj HIT-a, jeste prekid upotrebe heparina i prevođenje na drugu, alternativnu antikoagulantnu terapiju (ne na vitamin K oralne antikoagulanse), što se individualno određuje [39].

U svakodnevnoj kliničkoj praksi može se izračunati "HIT 4t" skor (trombocitopenija, vreme od uvođenja heparina do nastanka trombocitopenije, tromboze i ostale komplikacije, drugi uzroci trombocitopenije) radi brzog utvrđivanja verovatnoće nastanka HIT-a (skor od 0 - 3 poena predstavlja nizak rizik; skor od 4 - 5 poena predstavlja srednji rizik; skor od 6 - 8 poena predstavlja visok rizik). Ako je skor nizak, verovatnoća HIT-a je mala (indikovano je dalje praćenje), a ukoliko je u pitanju srednji ili visoki rizik, treba uraditi serološke testove (antiheparinska antitela) i započeti lečenje [40].

Dakle, antikoagulantna terapija, kao i praktično bilo koji drugi medikamentozni tretman, nosi određene rizike, pa je potrebno primeniti postulate savremene medicine i individualizovati terapiju u najvećoj mogućoj meri, te na vreme prepoznati i lečiti neželjena dejstva.

KORTIKOSTEROIDI U KOVID-19 INFEKCIJI

Još pre nastanka aktuelne pandemije, kortikosteroidi su predstavljali jedan od terapijskih izbora u lečenju akutnog respiratornog distres sindroma (ARDS) različite etiologije. Zbog toga je i sa pojavom KOVID-19 infekcije njihova upotreba postala tema velikog broja kliničkih istraživanja. S obzirom na patofiziološku osnovu ove bolesti, ali i farmakodinamiku kortikosteroida, njihova upotreba pokazala se kao opravdana. Međutim, kao posledica nedovoljne istraženosti svih patofizioloških mehanizama nastanka ove infekcije, kao i postojanja mogućnosti nastanka komplikacija usled primene kortikosteroidne terapije, mišljenja u vezi sa upotrebom ovih lekova ostala su podeljena [41]. Citokinska oluja je okarakterisana kao najteža komplikacija infekcije [42] koja nastaje kao posledica intenzivnog stvaranja proinflamatornih citokina usled disregulacije imunskog odgovora. Kortikosteroidi u našem organizmu ostvaruju primarno antiinflamatornu, ali i imunosupresivnu ulogu [43]. Na ovaj način oni redukuju oslobađanje glavnih medijatora citokinske oluje, tj. proinflamatornih citokina, supresijom gena koji su odgovorni za njihovu sintezu. Veliki broj studija ispitivao je efekte upotrebe kortikosteroida u lečenju pacijenata obolelih od KOVID-19 oboljenja. Ispitivana je uloga deksametazona, metilprednizolona i hidrokortizona. Multicentrična, nasumična studija, sprovedena u Velikoj Britaniji na 6.425 pacijenata, analizirala je uticaj primene deksametazona u dozi od 6 mg dnevno, intravenski ili oralno, u trajanju od 10 dana. Ustanovljeno je da je mortalitet u prvih 28 dana bio manji u grupi bolesnika koji su, uz standardnu

bleeding, hemodynamic support, transfusion of blood and blood derivatives, as well as hemostatic support need to be supplied, and the administration of appropriate antidotes (such as the use of vitamin K for vitamin K antagonists, protamine sulphate for heparin, etc.) needs to be considered [36]. Additionally, when heparin is applied, heparin-induced thrombocytopenia (HIT) may develop. It is an immunological reaction after drug use (most commonly unfractionated heparin, or less frequently LMWH) which leads to the prothrombotic state of the body, which is recognized by the development of thrombocytopenia in the space of a few days within the beginning of heparin therapy and the detection of antibodies to platelet-factor 4 [37,38]. HIT can be linked to pulmonary embolism, ischemic necrosis of the extremities (which requires amputation), acute myocardial infarction, as well as stroke. In case of suspicion of HIT development, it is of utmost importance that the application of heparin is discontinued and that the patient is put on other, alternative anticoagulant therapy (not vitamin K oral anticoagulants), which is determined individually, for each patient [39].

In everyday clinical practice the "HIT 4t" score can be calculated (thrombocytopenia, time from heparin introduction to thrombocytopenia development, thromboses and other complications, other thrombocytopenia causes) for rapid orientation regarding the probability of HIT development (a score of 0 - 3 points signifies low risk; a score of 4 - 5 points signifies medium risk; a score of 6 - 8 points signifies high risk). If the score is low, the probability of HIT is low (indicating the necessity for further monitoring), while if the score is medium or high, serological tests must be performed (antibodies against heparin) and treatment must be started [40].

Therefore, anticoagulant therapy, just like any other medicamentous treatment, carries certain risks, which is why it is necessary to apply the postulates of modern medicine and individualize the therapy, as much as possible, as well as recognize and treat its adverse effects.

CORTICOSTEROIDS IN COVID-19

Well before the ongoing pandemic, corticosteroids represented one of the therapeutic choices in the treatment of acute respiratory distress syndrome (ARDS) of different etiology. This is why, with the outbreak of COVID-19, their use has become the topic of a large number of clinical studies. Due to the pathophysiological basis of the disease, but also due to the pharmacodynamics of corticosteroids, their use has proven justified. However, as the result of insufficient understanding of all the pathophysiological mechanisms of the development of this infection, as well as due to the possibility of complications resulting from corticosteroid therapy, opinions regarding the use of these drugs

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terapiju, dobijali deksametazon. Takođe, pacijenti kod kojih je terapija deksametazonom započeta nakon sedmog dana bolesti, imali su bolju prognozu. Dokazano je i da najviše koristi od primene kortikosteroida imaju pacijenti sa umereno teškom i teškom formom bolesti, a koji koriste neki vid kiseoničke potpore. Ono što je zanimljivo je da, prema ovoj studiji, pacijenti sa lakšom formom bolesti, tj. formom koja ne zahteva upotrebu kiseoničke potpore, mogu češće ispoljiti neželjene efekte dejstva kortikosteroida, te je akcenat stavljen na individualnu procenu rizika i koristi od upotrebe kortikosteroida [44-46].

Kada je u pitanju primena metilprednizolona, studije GLUCOCOVID i MetCOVID ispitivale su njegovu kratkotrajnu upotrebu (GLUCOCOVID – 40 mg/12 h, a zatim 20 mg/12 h, intravenski, tokom tri dana; MetCOVID - 0,5 mg/kg/12 h, intravenski, pet dana) [47,48]. Pokazano je da je, kod bolesnika koji su, uz standardnu terapiju, dobijali i metilprednizolon, postojao niži rizik za prijem u jedinicu intenzivnog lečenja, manja potreba za neinvazivnom i invazivnom mehaničkom ventilacijom, kao i da je bio niži mortalitet. Pored navedenog, opšti zaključak svih studija je da davanje metilprednizolona skraćuje trajanje hospitalizacije, skraćujući vreme potrebno za oporavak i vreme trajanja potrebe za korišćenjem kiseoničke potpore. Poređenjem efekata deksametazona i metilprednizolona pokazalo se da je metilprednizolon superiorniji u odnosu na deksametazon, tako da su bolesnici koji su bili na terapiji metilprednizolonom ređe imali potrebu za mehaničkom ventilacijom, imali su niži mortalitet, kao i kraće trajanje hospitalizacije [49,50].

remain divided [41]. The cytokine storm, which occurs as the result of intensive production of proinflammatory cytokines, due to the dysregulation of immune response, has been characterized as the most severe complication of the infection [42]. In our body, corticosteroids have a primarily anti-inflammatory, but also an immunosuppressive role [43]. In this way, they reduce the release of major cytokine storm mediators, i.e., proinflammatory cytokines, by suppressing the genes responsible for their synthesis. Many studies have analyzed the effects of corticosteroid use in treating COVID-19 patients and have investigated the role of dexamethasone, methylprednisolone, and hydrocortisone. A multicentric, randomized study, carried out in Great Britain, on 6,425 patients, analyzed the effect of dexamethasone application, 6 mg/day, intravenously or orally, for 10 days. It was found that mortality in the first 28 days was lower in the group of patients who, along with standard therapy, received dexamethasone. Also, patients who were put on dexamethasone after the seventh day of disease onset, had a better prognosis. It has been proven that patients with the moderately severe and the severe form of the disease, who were on some form of oxygen therapy, benefitted the most from corticosteroid application. What is interesting is the fact that, according to this study, patients with the milder form of the disease, i.e., a form that did not require oxygen therapy, more frequently exhibited adverse reactions to corticosteroid effects, which is why the need for individual risk and benefit assessment in the application of corticosteroids was stressed as important [44-46].

Tabela 2. Sistematizovani pregled studija koje su ispitivale efekat deksametazona i hidrokortizona sa prikazanim zaključcima [53]

Studija/Autor	Tip studije	N	Lek	Doza	Put	Trajanje (dani)	Zaključak
RECOVERY TRIAL	Randomizovana multicentrična prospektivna	6.425	D	6 mg/dan	iv/p.o.	10	-niži mortalitet kod težih formi i onih na kiseoničkoj potpori -bolji ishod ako se terapija započne posle 7. dana bolesti -trajanje terapije duže od 10 dana samo kod teških formi i rizika od fibroze -kod blagih formi i osoba sa komorbiditetima veći rizik od neželjenih efekata
CoDEX	Randomizovana retrospektivna	299	D	20 mg/dan pa 10 mg/dan	iv	5+5	-bez dokazane razlike u mortalitetu među grupama
DEXA-COVID19	Randomizovana multicentrična open-label	200	D	20 mg/dan pa 10 mg/dan	iv	5+5	-rezultati još uvek u radu
CAPE-COVID	Randomizovana multicentrična prospektivna dvostruko slepa	149	H	200 mg/dan	iv	10	-ređe nastajanje respiratorne insuficijencije, potrebe za MV-om (ali bez dokazane statističke značajnosti)
REMAP-CAP	Randomizovana multinacionalna platforma za ispitivanje vanbolničkih pneumonija	403	H	50 mg/6 h	iv	8 – 14	-bolje preživljavanje u grupi koja je dobijala hidrokortizon

N – broj pacijenata; D – deksametazon; M – metilprednizolon; H – hidrokortizon; iv – intravenski; p.o. – per os (oralno); NIV – neinvazivna ventilacija; MV – mehanička ventilacija

preuzeto iz: Milenković M, Đukić M, Brajković M, Klašnja S, Tošković B, Zdravković M. Primena kortikosteroida u terapiji COVID-19 infekcije SJAIT.2021;(43)VII – IX) [53]

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Table 2. Systematized overview of studies which have analyzed the effect of dexamethasone and hydrocortisone, with presented conclusions [53]

Study/Author	Type of study	N	Drug	Dose	Method of administration	Duration (days)	Conclusion
RECOVERY TRIAL	Randomized multicentric prospective	6,425	D	6 mg/day	iv/p.o.	10	-lower mortality in severe forms and in patients on oxygen support -better outcome if the therapy is started after the seventh day of illness -duration of therapy longer than 10 days only in severe forms and when there is risk of fibrosis -in mild forms and individuals with comorbidities - greater risk of adverse effects
CoDEX	Randomized retrospective	299	D	20 mg/day then 10 mg/day	iv	5+5	-without proven difference in mortality amongst groups
DEXA-COVID19	Randomized multicentric open-label	200	D	20 mg/day then 10 mg/day	iv	5+5	-results still being processed
CAPE-COVID	Randomized multicentric prospective double-blind	149	H	200 mg/day	iv	10	-less frequent occurrence of respiratory insufficiency; less need for MV (but without proven statistical significance)
REMAP-CAP	Randomized multicentric platform for assessing pneumonia cases outside the hospital	403	H	50 mg/6 h	iv	8 – 14	-better survival in the group receiving hydrocortisone

N – number of patients; D – dexamethasone; M – methylprednisolone; H – hydrocortisone; iv – intravenous; p.o. – per os (orally); NIV – noninvasive ventilation; MV – mechanical ventilation
(from: Milenković M, Đukić M, Brajković M, Klašnja S, Tošković B, Zdravković M. Primena kortikosteroida u terapiji COVID-19 infekcije SJAIT.2021;(43)VII – IX) [53]

Najmanje ispitivan, ali svakako ne najmanje bitan, jeste hidrokortizon. Fiksne, male doze hidrokortizona utiču na bolje preživljavanje pacijenata u prvih 21 dan bolesti [51,52]. Osim toga, kod ovih pacijenata rjeđe nastupa respiratorna insuficijencija, potreba za mehaničkom ventilacijom, kao i smrtni ishod, ali nije utvrđena statistička značajnost ovih rezultata.

Sve u svemu, bilo koji od kortikosteroida da se daje u terapiji KOVID-19 oboljenja, važno je da ga ne treba ordinirati na samom početku bolesti, već kada postane jasno, na osnovu kliničkog toka i rezultata laboratorijskih analiza, u kom pravcu se bolest razvija. Lake forme bolesti ne zahtevaju davanje kortikosteroida (Tabele 2 i 3).

ZAŠTO SU MIŠLJENJA O UPOTREBI KORTIKOSTEROIDA PODELJENA?

Kao i drugi lekovi i supstance, kortikosteroidi tokom upotrebe mogu ispoljiti neželjena dejstva. Najčešće dolazi do poremećaja glikoregulacije kod pacijenata koji već boluju od diabetes mellitus-a, ali nije retka ni pojava poremećaja glikoregulacije kod ostalih pacijenata [54]. S obzirom da kortikosteroidi predstavljaju fiziološki produkt nadbubrega, njihov unos može voditi u adrenalnu supresiju, koja se može manifestovati adrenalnom krizom, ali i jatrogenim Kušingovim sindromom [54]. Takođe, česte su i komplikacije na nivou kardiovaskularnog sistema i to najčešće u vidu hipertenzije, ishemijske bolesti srca i hiperlipidemije [55].

Regarding the application of methylprednisolone, the GLUCOCOVID and MetCOVID studies examined its short-term use (GLUCOCOVID – 40 mg/12 h, and then 20 mg/12 h, intravenously, over a period of three days; MetCOVID – 0.5 mg/kg/12 h, intravenously, over a period of five days) [47,48]. It has been shown that, in patients who, in addition to standard therapy, also received methylprednisolone, there was a lower risk of being admitted to the ICU, a lesser need for noninvasive and invasive mechanical ventilation, as well as lower mortality. Additionally, the universal conclusion of all the studies was that methylprednisolone application shortened hospital stay, by shortening the time necessary for recovery as well as the duration of necessary oxygen support. The comparison of the effects of dexamethasone and methylprednisolone demonstrated the superiority of methylprednisolone over dexamethasone, which is why patients who received methylprednisolone therapy less commonly had the need for mechanical ventilation, they had lower mortality, as well as a shorter stay in hospital [49,50].

The least researched, but certainly not the least important, is hydrocortisone. Fixed, small doses of hydrocortisone affect better survival of patients in the first 21 days of illness [51,52]. Additionally, in these patients, respiratory insufficiency occurs less frequently, as does the need for mechanical ventilation and the lethal outcome, however, the statistical significance of these results has not been confirmed.

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Tabela 3. Sistematizovani pregled studija koje su ispitivale dejstvo metilprednizolona i upoređivale ga sa efektom deksametazona, sa prikazanim zaključcima [53]

Studija/Autor	Tip studije	N	Lek	Doza	Put	Trajanje (dani)	Zaključak
GLUCOCOVID	Parcijalno randomizovana multicentrična	85	M	40 mg/12 h pa 20 mg/12 h	iv	3+3	-niži rizik za prijem u JIL; manja potreba za NIV-om i MV-om; niži mortalitet
MetCOVID	Randomizovana dvostruko slepa placebom kontrolisana IIb faza	647	M	0,5 mg/kg/12 h	iv	5	-niži mortalitet kod starijih od 65 godina
Ranjbar i sar. [49]	Randomizovana prospektivna trostruko slepa	86	M D	1 - 2 mg/kg/dan 6 mg/dan	iv	10	-bolesnici koji su dobijali M oporavili su se u većem procentu; potreba za MV-om i trajanje hospitalizacije manji nego kod onih koji su dobijali D
Ko i sar. [50]	Pregledni rad	262	M D	1 mg/kg/dan 6 mg/dan	iv	≥3 ≥7	-mortalitet u grupama koje su dobijale kortikosteroide je bio značajno niži, posebno kod onih lečenih M-om

N – broj pacijenata; D – deksametazon; M – metilprednizolon; H – hidrokortizon; iv – intravenski; p.o. – per os (oralno); NIV – neinvazivna ventilacija; MV – mehanička ventilacija
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Table 3. Systematized overview of studies which have analyzed the effect of methylprednisolone and compared it to the effect of dexamethasone, with presented conclusions [53]

Study/Author	Type of study	N	Drug	Dose	Method of administration	Duration (days)	Conclusion
GLUCOCOVID	Partially randomized multicentric	85	M	40 mg/12 h then 20 mg/12 h	iv	3+3	-lesser risk for being admitted into the ICU; less need for NIV and MV; lower mortality
MetCOVID	Randomized double-blind placebo-controlled phase IIb	647	M	0.5 mg/kg/12 h	iv	5	-lower mortality in patients older than 65 years
Ranjbar et al. [49]	Randomized prospective triple-blind	86	M D	1 - 2 mg/kg/day 6 mg/day	iv	10	-a higher percentage of patients receiving M recovered; the need for MV and the duration of hospitalization was lesser, i.e., shorter, than in patients receiving D
Ko et al. [50]	Review article	262	M D	1 mg/kg/day 6 mg/day	iv	≥3 ≥7	-the mortality in groups receiving corticosteroids was significantly lower, especially in those treated with M

N – number of patients; D – dexamethasone; M – methylprednisolone; H – hydrocortisone; iv – intravenous; p.o. – per os (orally); NIV – noninvasive ventilation; MV – mechanical ventilation
(from: Milenković M, Đukić M, Brajković M, Klašnja S, Tošković B, Zdravković M. Primena kortikosteroida u terapiji COVID-19 infekcije SJAIT.2021;(43)VII – IX) [53]

Većina ovih neželjenih efekata je dozno zavisna, a osim toga, osobe sa pojedinim stanjima imaju veću sklonost ka razvoju komplikacija. Zato je bitno još jednom naglasiti važnost individualne procene odnosa korist – rizik, pre donošenja odluke o započinjanju kortikosteroidne terapije.

ZAKLJUČAK

Ovaj rad imao je za cilj da pokaže važnost upotrebe antikoagulantne i kortikosteroidne terapije u lečenju KOVID-19 infekcije. S obzirom na globalnu važnost rešavanja pandemije, naglasak je stavljen na lečenje već nastale infekcije i njenih komplikacija, za šta su bitne ove dve grupe lekova. Antikoagulantna terapija primenjuje se u lečenju hospitalizovanih pacijenata obolelih od infekcije prouzrokovane SARS-KoV-2 virusom. U slučaju vanbolničkog lečenja ove infektivne bolesti,

All in all, whichever corticosteroid is administered in the treatment of COVID-19, it is important that it should not be given at the very beginning, but when it becomes clear, based on the clinical course of the disease and the laboratory analyses, which direction the disease is taking. Mild forms of the disease do not require the application of corticosteroids (Tables 2 and 3).

WHY ARE OPINIONS ON THE USE OF CORTICOSTEROIDS DIVIDED?

As is the case with other drugs and substances, corticosteroids may exhibit adverse effects. The most commonly occurring adverse effect is the disturbance of glucoregulation in patients already suffering from diabetes mellitus, however, this complication may also occur in other patients [54]. Bearing in mind that cor-

ne preporučuje se korišćenje antiagregacione i antiko-agulantne terapije. S obzirom na postojanje rizika od nastanka različitih neželjenih efekata, poput krvarenja i trombocitopenije uzrokovane heparinom, potreban je individualni pristup svakom pacijentu i pažljivo or-diniranje antikoagulantne terapije, uz praćenje njenih efekata.

Što se tiče upotrebe kortikosteroida, naglasak je na njihovoj efikasnosti kod pacijenata sa umereno teškom i teškom kliničkom slikom koji zahtevaju neki vid ki-seoničke potpore. Ta efikasnost se ogleda u snižavanju mortaliteta, smanjenju potreba za mehaničkom venti-lacijom i potreba za prevođenjem u jedinice intenziv-nog lečenja, kao i u kraćem trajanju hospitalizacije. Kao najpotentniji pokazao se metilprednizolon, mada su za takvu tvrdnju potrebne dalje studije, s obzirom da je poznato da upotreba kortikosteroida nosi sa sobom ri-zik neželjenih efekata, koji se kod nekih kategorija bo-lesnika, ili pri određenim dozama, češće očekuju.

Na kraju, važno je istaći da je individualna proce-na koristi i rizika, pri uključivanju ovih lekova u terapiju bolesnika sa potvrđenom KOVID-19 infekcijom, od vi-talnog značaja za postizanje željenih efekata terapije.

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ticosteroids are a physiological product of the adrenal glands, their intake may lead to adrenal suppression, which may manifest as adrenal crisis, but also as iat-rogenic Cushing's syndrome [54]. Complications at the level of the cardiovascular system are also frequent, most commonly in the form of hypertension, ischemic heart disease, and hyperlipidemia [55]. Most of these adverse effects are dose-dependent, and, additionally, individuals with certain conditions have a higher ten-dency towards developing complications. This is why it is important, once more, to emphasize how significant it is to individually assess the benefit – risk ratio before making a decision on starting corticosteroid treatment.

CONCLUSION

The aim of this paper is to demonstrate the importance of the application of anticoagulant and corticosteroid therapy in the treatment of COVID-19. Bearing in mind the global importance of resolving the pandemic, em-phasis is placed on treating the already existing infec-tion and its complications, for which these two groups of drugs are important. Anticoagulant therapy is ap-plied in the treatment of hospitalized patients suffer-ing from the disease caused by the SARS-CoV-2 virus. When people suffering from this infectious disease are treated as outpatients, the use antiaggregation and anticoagulant therapy is not recommended. Bearing in mind the risk of the development of different adverse effects, such as bleeding and heparin-induced throm-bocytopenia, an individualized approach to each pa-tient as well as careful prescribing of anticoagulant therapy is necessary, as is the monitoring of its effects.

As far as the application of corticosteroids is con-cerned, the emphasis is on their efficiency in patients with moderate and severe clinical presentation which require some form of oxygen support. This efficiency is manifested in the decrease of mortality, the reduction of the need for mechanical ventilation and the reduc-tion of the need for transferring patients to intensive care units, as well as in the shortened duration of hos-pitalization. Methylprednisolone has proven to be the most potent, although further studies are necessary to prove this, since it is known that the use of corticoste-roids carries the risk of adverse effects, which, in cer-tain categories of patients, or with certain doses, are expected more frequently.

Finally, it is important to emphasize that the indi-vidual assessment of benefits and risks, when these drugs are included in the treatment of patients with confirmed COVID-19, is of vital importance for achiev-ing the desired effects of the therapy.

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