Archives of Anesthesiology and Critical Care (Summer 2022); 8(3): 263-266.

Available online at http://aacc.tums.ac.ir

Letter to Editor

Anticoagulant Therapy Is a Contentious Issue in COVID-19 Patients

Hesam Aldin Varpaei[1], Mostafa Mohammadi[2]*, Shima Loni[3], Seyedeh Yasaman Hashemi-Amir[3]

[1]Department of Surgical Nursing, Faculty of Nursing, Near East University,, Nicosia, Cyprus.

[2]Department of Anesthesiology and Critical Care, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.

[3]Department of Internal Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

Article history:
Received 15 January 2022
Revised 05 February 2022
Accepted 19 February 2022

Despite various research around the world regarding SARS-Cov2, the pathophysiology of the disease is still unknown [1]. From SARS-Cov 2 can arise the cytokine storm that causes generalized inflammation. The inflammation causes coagulation in lung capillaries and microthrombosis that damage the lungs and cause a poor outcome [2]. In a non-critical setting, it is reported that patients treated with therapeutic doses of anticoagulants experienced more bleeding events in comparison to patients treated with standard prophylactic doses, but overall mortality rates were relatively unchanged [3]. It should be mentioned that, in spite of the large sample size of this study (n = 324), it did not follow a well-matched and homogenous population (240 treated with a prophylactic dose of anticoagulant versus 84 treated with therapeutic doses). Although in the critical care setting, COVID-19 patients are at the risk of thrombotic events [4] and might receive thromboprophylaxis or even anticoagulation therapy, they are also exposed to the risk of hemorrhagic events [5].

Anticoagulation therapy in severe COVID-19 is accompanied by a better prognosis in patients who have sepsis-induced coagulopathy score >=4 and/or D-dimer more than 6 times the upper limit of normal. The interim guideline of the International Society of Thrombosis and Hemostasis has advocated a prophylactic dose of Low Molecular Weight Heparin (LMWH) in all COVID-19 patients who are admitted to the hospital [6].

Klok et al. [7] in a recent article point out that the incidence of thrombotic complications in COVID-19 intensive care unit (ICU) patients is 31%, which is remarkably high. Therefore, it may need higher thromboprophylaxis doses of heparin or LMWH in severe COVID-19 cases. Thromboembolic events in critically ill COVID-19 patients are higher with prophylactic anticoagulation compared with therapeutic regimes. In COVID-19 ICU patients, venous thromboembolism is reported even in patients under therapeutic doses of anticoagulants, so it is reasonable to consider both early screening and therapeutic anticoagulation for VTE in critically ill COVID-19 patients [8]. However, it should not be underestimated that the study was performed with a limited sample size (total n = 26, n = 8 for prophylactic anticoagulation at admission versus n = 18 for therapeutic anticoagulation at admission). A study by Stessel et al [9] showed that the cumulative risk of VTE and mortality may be reduced by more aggressive thromboprophylaxis protocols, which include close to therapeutic LMWH doses with daily monitoring of anti-Xa activity and ultrasonography for screening of Deep Venous Thromboembolism twice per

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: mohammady_mm@tums.ac.ir

week. Selection of the appropriate dose of prophylactic anticoagulant based on risk stratification is a reasonable approach. Patients with a severe inflammatory syndrome and/or hypercoagulopathy (elevated d-dimmer and/or fibrinogen), patients with a BMI greater than 30 and an additional risk factor for thromboembolism, patients on mechanical ventilation or high-flow nasal O2 therapy, patients on extracorporeal membrane oxygenation (ECMO), and patients with unexplained thrombosis of catheter or dialysis filter thrombosis are all at high risk. The recommendation for these patients is to receive heparin or LMWH in therapeutic doses [10]. Routine prophylactic doses of anticoagulants may be insufficient for thromboprophylaxis in severe COVID-19.

All the above studies might convince us that anticoagulant therapy is needed for all COVID-19 patients and even reduce mortality, hospitalization, and the need for mechanical ventilation. Controversially, the primary study revealed that anticoagulant or antiplatelet prescription at the time of infection would not change the mortality of COVID-19 patients [11]. However, that was a study with a limited sample size (n = 29). Later on, a study [12] showed that antiplatelet medication did not significantly change the outcomes or need for mechanical ventilation. Although this study was conducted on 152 patients, the population was not balanced and homogeneous (21 patients on mechanical ventilation versus 131 patients without it). Recently, the results of a meta-analysis [13] confirmed that antiplatelet agents might not change mortality. The important tip for clinicians is that since prevention and treatment of venous and arterial thrombosis in COVID-19 patients is within the narrow therapeutic index, close monitoring should be considered [14] (e.g., check partial thrombin time (PTT) every 4–6 hours or anti-Xa factor). Implicitly, a report showed that despite systemic anticoagulant therapy in critically ill COVID-19 patients, 15 percent of patients experienced deep vein thrombosis [15]. In continuing, the results of a randomized clinical trial (RCT) [16] with a large sample size (n = 562) and homogeneous patients in each group revealed that intermediate-dose prophylactic anticoagulation in comparison to standard-dose prophylactic anticoagulation did not change overall mortality or the incidence of venous or arterial thrombosis. It should be taken into account that this study insists on the use of enoxaparin in the critical care setting. Nevertheless, heparin is used more frequently in ICUs (bolus injection or drip infusion) [17]. This is because, in the critical care setting, clinicians tend to prescribe intravenous medications such as heparin. Due to heparin pharmacokinetics and pharmacodynamics, the subcutaneous injection has low efficacy in critically ill patients. It has a low cost and can be screened by PTT. Yet, the use of heparin (prophylactic or therapeutic) for COVID-19 critically ill patients is not well-known.

Direct oral anticoagulants (DOAC) are another choice for clinicians for the prevention or treatment of coagulation in COVID-19 patients. DOAC interacts with a variety of COVID-19 medications, including IL6-blocking receptor agents (e.g., Tocilizumab or Sarilimab) [18], dexamethasone, and numerous antiviral agents. DOACs interact with P-glycoprotein and/or cytochrome P450, which can cause a change in DOAC activity. Therefore, it is advised not to start or continue DOACs in COVID-19 patients [19]. However, the result of a cohort study on COVID-19 ICU patients stated that Apixaban was used as therapeutic anticoagulation in COVID-19 patients with suspected or confirmed VTE or AF rhythm. Apixaban has been recognized as safe and efficacious in severe COVID-19 cases [20]. It should be noted that the study was limited to just 21 ICU patients who mostly (86%) received heparin or low molecular weight heparin 24 hours before Apixaban. Besides, no patients experienced bleeding events. According to the interaction of DOAC with other COVID-19 treatments (particularly "dexamethasone," which is one of the most basic treatments for COVID-19), it seems that it could not be the first choice and needs a higher level of screening. But this is the primary hypothesis, and more studies are needed.

The utilization of anticoagulants in COVID-19 patients, specifically in critical care, is controversially unclear. Although COVID-19 patients are at the risk of micro coagulation, especially when pulmonary capillary anticoagulant medications (whether injection or oral) are necessary, these agents did not show a significant difference in in-hospital mortality or the need for mechanical ventilation. Besides, antiplatelets and anticoagulants put patients at the risk of bleeding (hematuria, gastrointestinal bleeding, tracheal bleeding), which might exacerbate the circumstance or cause death.

In a RCT by Patrick R. Lawler et al [21], the survival and time of discharge from the hospital were compared between two groups of noncritically ill patients with COVID-19 disease. Non-critically ill COVID-19 disease was defined as a moderately ill disease that needed hospitalization but didn’t need advanced respiratory support (oxygen with high nasal flow, non-invasive ventilation, invasive mechanical ventilation) and other organ support. The group that received therapeutic dose anticoagulation with heparin had better survival and less need for ICU care compared with the other group that received heparin with a prophylactic dose. This article advocated that therapeutic anticoagulation can have a better outcome in non-critically ill hospitalized patients at any baseline level of d-dimer. The results of an RCT by Ewan C. Gholiger et al [22] showed that therapeutic anticoagulation with unfractionated heparin or low molecular weight heparin had no superiority in pharmacological thromboprophylaxis in critically ill COVID-19 patients. In this multicenter study, critically

ill COVID-19 patients were defined as patients who needed advanced respiratory support or cardiovascular organ support in the ICU. Therapeutic anticoagulation with unfractionated heparin or low molecular weight heparin didn't have any benefit in terms of survival and shortening the duration of respiratory or cardiovascular support in comparison with prophylactic anticoagulation. Major bleeding complications were higher with therapeutic anticoagulation compared with usual pharmacologic thromboprophylaxis.

It seems that an RCT with well-matched patients and a large sample size (n = 30 in each group) is required to assess the advantages and disadvantages of anticoagulant/antiplatelet therapy in critically-ill patients. Preferably, the intervention consists of both antiplatelet and anticoagulant agents. Also, either low molecular weight heparin or heparin should be included in the study.

According to the most recent NIH guidelines [24], a prophylactic dose of heparin as thromboembolic event prophylaxis is recommended in hospitalized adults in ICU (consider any contraindications). If a patient starts on a therapeutic dosage of heparin in a non-ICU environment because to COVID-19 and then transfers to the ICU, the Panel advises moving from the therapeutic dose to a preventive dose of heparin, until VTE is verified.

To conclude, it seems that in critically ill COVID-19 patients with a high risk of thrombosis, heparin infusion with specific targeted PTT and screening with ultrasonography [23] can be an appropriate choice. Based on evidence and local protocols [25], we prefer a prophylactic dose of heparin (infusion rather than subcutaneous) with targeted PTT (Max45) [26]. For other COVID-19 patients with mild to moderate risk, a prophylactic dose of heparin or low molecular weight heparin can be prescribed. Once again, more studies are needed to confirm it.

References

[1] Mohammadi M, Hadian M R, Varpaei H A. Exercise in COVID-19: Intensity and Timing. Asian J Sports Med.12(3):e113266.

[2] Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. The Lancet Respiratory Medicine. 2020; 8(6):e46-7.

[3] Pesavento R, Ceccato D, Pasquetto G, Monticelli J, Leone L, Frigo A, et al. The hazard of (sub) therapeutic doses of anticoagulants in non- critically ill patients with Covid- 19: The Padua province experience. J Thromb Haemost.. 2020; 18(10):2629-35.

[4] Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020. 46(6):1089-1098.

[5] Fraissé M, Logre E, Pajot O, Mentec H, Plantefève G, Contou D. Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study. Critical Care. 20200; 24(1):275.

[6] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18(5):1094-1099.

[7] Klok FA, Kruip MJ, Van der Meer NJ, Arbous MS, Gommers DA, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020; 191:145-7.

[8] Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID- 19 patients. J Thromb Haemost. 2020; 18(7):1743-6.

[9] Stessel B, Vanvuchelen C, Bruckers L, Geebelen L, Callebaut I, Vandenbrande J, et al. Impact of implementation of an individualised thromboprophylaxis protocol in critically ill ICU patients with COVID-19: A longitudinal controlled before-after study. Thromb Res. 2020; 194:209-15.

[10] Susen S, Tacquard CA, Godon A, Mansour A, Garrigue D, Nguyen P, et al. Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring. Crit Care. 2020; 24(1):364.

[11] Sivaloganathan H, Ladikou EE, Chevassut T. COVID- 19 mortality in patients on anticoagulants and antiplatelet agents. Br J Haematol. 2020; 190(4):e192-5.

[12] Banik J, Mezera V, Köhler C, Schmidtmann M. Antiplatelet therapy in patients with Covid-19: A retrospective observational study. Thrombosis Update. 2021; 2:100026.

[13] Wang Y, Ao G, Nasr B, Qi X. Effect of antiplatelet treatments on patients with COVID-19 infection: A systematic review and meta-analysis. Am J Emerg Med. 2021; 43:27-30.

[14] Watson RA, Johnson DM, Dharia RN, Merli GJ, Doherty JU. Anti-coagulant and anti-platelet therapy in the COVID-19 patient: a best practices quality initiative across a large health system. Hosp Pract (1995). 2020; 48(4):169-179.

[15] Nahum J, Morichau-Beauchant T, Daviaud F, Echegut P, Fichet J, Maillet JM, et al. Venous Thrombosis Among Critically Ill Patients With Coronavirus Disease 2019 (COVID-19). JAMA Netw Open. 2020; 3(5):e2010478.

[16] Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted

to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA. 2021; 325(16):1620-1630. https://10.1001/jama.2021.4152

[17] Izadpanah M, Khalili H, Mohammadi M. Comparing safety of heparin as continuous intravenous infusion and multiple subcutaneous injections. J Comp Eff Res. 2016; 5(1):31-8.

[18] El-Ghiaty MA, Shoieb SM, El-Kadi AOS. Cytochrome P450-mediated drug interactions in COVID-19 patients: current findings and possible mechanisms. Med Hypotheses. 2020; 144:110033.

[19] Schutgens RE. DOAC in COVID-19: Yes or No?. HemaSphere. 2020; 5(1):e526.

[20] Wenzler E, Engineer MH, Yaqoob M, Benken ST. Safety and Efficacy of Apixaban For Therapeutic Anticoagulation in Critically Ill ICU Patients with Severe COVID-19 Respiratory Disease. TH open. 2020; 4(4):e376-e382.

[21] REMAP-CAP, ACTIV-4a, ATTACC Investigators, Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med. 2021; 385(9):777-89.

[22] ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators, Lawler PR, Goligher EC, Berger JS, Neal MD, Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med. 2021; 385(9):790-802.

[23] Voicu S, Chousterman BG, Bonnin P, Deye N, Malissin I, Le Gall A, et al. Increased anticoagulation reduces proximal deep vein thrombosis in mechanically ventilated COVID-19 patients: Venous thrombosis prevention & COVID-19. J Infect. 2021 May;82(5):186-230.

[24] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed February 24, 2022

[25] Hussain Khan Z, Maki Aldulaimi A, Varpaei H, Mohammadi M. Various Aspects of Non-Invasive Ventilation in COVID-19 Patients: A Narrative Review. Iranian J Med Sci, 2022; 47(3): 194-209.

[26] Hossein Dokht A, Varpaei HA, Mohammadi M, Amiri H. Upper limb deep vein thromboembolism: a case report. Medical Science Journal of Islamic Azad Univesity-Tehran Medical Branch. 2021; 31(4):459-63.