Asian Journal of Biomedical and Pharmaceutical Sciences *ISSN: 2249-622X*

Mini Review: Heparin treatment in COVID-19: Where are we?

Rizzo M, Pezone I, Amicone M, Riccio E, Pisani A*

Department of Public Health, Nephrology Unit, University of Naples "Federico II", 80131 Naples, Italy

Abstract

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome with a high mortality rate; it is caused by SARS-CoV-2, a new virus of the *Coronaviridae* family that emerged in Wuhan, Hubei, China, in December 2019 and rapidly spread worldwide until declared by the World Health Organization a global pandemic on March 11th, 2020. The race for an effective drug to prevent or treat SARS-CoV-2 infection is the highest priority among health care providers, government officials, and the pharmaceutical industry. Despite scientific effort, no pharmacological intervention has proven definitively beneficial, and care is primarily supportive.

Keywords: Coronavirus disease, *Coronaviridae*, SARS-CoV-2, High mortality rate.

Accepted on October 01, 2020

Description

Heparin role in COVID-19 management is currently under debate [1-3]. Heparin (in the form of unfractionated heparin UFH or low molecular weight heparin LMWH, comprising several chemically distinct compounds) is mainstay treatment in thrombotic disorders. LMWH is increasingly supplanting UFH owing to a number of advantages, including a more predictable pharmacokinetic profile with increased bioavailability and the need for less frequent administration and decreased risk of bleeding. Moreover, in contrast to UFH, anticoagulant monitoring with partial thromboplastin time (aPTT) is not usually required with LMWH.

Heparin has been extensively used in COVID-19 management due to its anticoagulant properties, mostly as LMWH at prophylactic dose in complicated patients with increased thrombotic risk [4].

Hypercoagulable state in COVID-19 patients is associated with both venous and arterial thrombosis, with pulmonary embolism, stroke, acute limb ischemia, acute coronary syndromes, and recurrent clotting of dialysis filters or oxygenators of extracorporeal membrane oxygenation.

COVID-19 coagulopathy typically presents in critically ill patients with thrombocytopenia, prolongation of Prothrombin Time (PT), prolongation of partial thromboplastin time (aPTT), elevated serum D-dimer and elevated fibrinogen

In these patients, anticoagulation benefits are well-established. A retrospective analysis conducted in Tongji hospital showed that LMWH use is associated with better outcomes in severe COVID-19 patients meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimer [5].

As revealed by autopsy studies [6], coagulopathy represents a common complication in patients with severe COVID-19, for surprisingly high incidence of deep venous thrombosis and pulmonary embolism was observed at post-mortem examination. It's interesting to note that thromboembolic events were sometimes clinically overlooked, and sudden and unexplained deaths in critically ill patients correlated with suggestive autopsy findings. In addition, microthrombi were found in the pulmonary microvasculature, possibly explaining ventilation-perfusion mismatch and subsequent refractory hypoxemia in these patients [7]. Anatomic location of capillary obstruction also matches the predominantly distal and patchy distribution of the radiological infiltrates [8].

Thus, coagulopathy may play an important part in COVID-19 natural history.

Several pathogenetic mechanisms are involved in COVID-19 coagulopathy, which can be classified as a consumptive coagulopathy. Those include direct viral damage and inflammatory effect by cytokine storm on the endothelium or coagulation cascade. It is likely that additional mechanisms may also contribute to the pathogenesis of hemostatic imbalance, such as immune-mediated damage by anti-phospholipid antibodies. Moreover, hypoxia itself, long term bed rest and possible hormone treatment increase thromboembolic risk. Eventually, free thrombin activates platelets and stimulates fibrinolysis with elevated levels of D-dimer and fibrinogen degradation products.

The largest available study evaluating anticoagulation in COVID-19 is an analysis of 2,773 patients in the Mount Sinai Health System in New York City [9]. Results proved that systemic treatment-dose anticoagulation in COVID-19 patients is associated with reduced in-hospital mortality and longer median survival. In addition, though patients who received treatment-dose anticoagulation were more likely to require invasive mechanical ventilation, probably reflecting reservation of treatment-dose anticoagulation for more severe clinical presentations, they showed better outcomes than mechanical ventilation-treated patients not receiving treatment-dose anticoagulation.

Treatment-dose heparin tailored to clinical severity were also associated with significant improvement observed in oxygen

exchange and clinical symptoms in 27 consecutive COVID-19 patients admitted to Sirio Libanes Hospital in São Paulo-Brazil [10].

Another retrospective clinical study evaluating 44 COVID-19 patients [11], showed significant increase in percentage of lymphocytes and reduction of D-dimer, FDP and IL-6 levels in COVID-19 patients treated with LMWH compared to control subjects.

Initial observations also address the possible differences between UFH and LMWH in COVID-19 patients. Though UFH should be preferred in marked renal impairment, heparin resistance caused by markedly increased acute phase reactants including fibrinogen could limit its use. Other than systemic heparin, nebulised UFH was also proposed for COVID-19 pneumonia and ARDS [12,13].

Note that, in addition to anticoagulation, heparin rationale against COVID-19 seem to be supported at least by two additional modes of activity: Anti-inflammatory and antiviral.

In particular, heparin may exhibit antiviral properties against SARS-CoV-2, inhibiting initial infection or spread from infected to non-infected cells.

Heparin antiviral properties against several viral pathogens are known, including hepatitis C virus and herpesvirus family.

Antiviral efficacy against *Coronaviridae* family was first revealed in a 2011 experiment in which heparin prevented SARS-CoV pseudovirus entry into host cells [14].

According to this model, cell surface heparan sulfate interacts with SARS-CoV spike protein as an adhesion molecule coreceptor, as the bond facilitates SARS-CoV interaction with ACE2 receptor and subsequent cell entry. Specifically, heparin acts as a decoy receptor for SARS-CoV spike protein, diverting virus from cell surface. Based on these premises, heparin ability to bind SARS-CoV-2 was tested. It was demonstrated that heparin effectively binds to SARS-CoV-2 spike protein and induces a significant structural change [15]. A recent in vitro experiment also confirmed that heparin in vitro prevents SARS-CoV-2 infection [16]. Apparently, antiviral activity through competitive spike protein binding is less evident with LMWH than UFH [17].

Conclusion

In conclusion, though heparin benefits are well-established in severe COVID-19 patients with increased thromboembolic risk, its additional theoretic properties (anti-inflammatory and antiviral) taken together with growing clinical data seem to suggest a broader use. Multi-centre, randomized controlled trials are mandatory to answer unresolved questions, including optimal anticoagulant dose with possible utilization of therapeutic anticoagulation before the development of thrombosis, potential differences between UFH and LMWH and patient characteristics to balance benefits and risks (above all hemorrhagic risks).

Heavy metals and organic compounds can be accumulated in aquatic biota. Bioaccumulation is the net build-up of substances from water in an aquatic organism as a result of enhanced uptake and slow elimination of such substance. Bioaccumulation measurements of heavy metals are very important because of their deleterious effect on the aquatic ecosystems. The characteristics of some heavy metals are the strong attraction to the biological tissue and their slow elimination from biological system. Since fish can occupy different tropic level they found to be good indicator of heavy metal contamination levels in aquatic system. Similar study by Azmat et al., also confirms fishes as one of the most significant indicators in fresh water systems for the estimation of metal pollution. The toxicity level of heavy metals depend on the detoxification rate of metals, the habitat of the fish and concentration level of elements in the food.

References

1. Hippensteel JA, LaRiviere WB, Colbert JF, et al. Heparin as a Therapy for COVID-19: Current Evidence and Future Possibilities. Am J Physiol Lung Cell Mol Physiol. 319: L211-L217.
2. Thachil, Jecko. The versatile heparin in COVID-19. J Thromb Haemost. 2020; 18:1020-1022.
3. Liu, Jian, et al. Using heparin molecules to manage COVID-2019. Res Pract Thromb Haemost. 2020; 4: 518–523.
4. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18:1023-1026.
5. Ning Tang, Huan Bai, Xing Chen, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18:1094-1099.
6. Dominic Wichmann, Jan-Peter Sperhake, Marc Lütgehetmann, et al. Autopsy findings and venous thromboembolism in patients with covid-19: A prospective cohort study. Ann Intern Med. 2020; M20-2003.
7. Yao XH, Li TY, He ZC, et al. A pathological report of three covid-19 cases by minimal invasive autopsies. Zhonghua Bing Li Xue Za Zhi. 2020; 49: 411-417.
8. Ye Zheng, Zhang Yun, Wang Yi, et al. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): A Pictorial Review. Europ Radiol. 2020; 30: 4381-4389.
9. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation within hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020; 7; 76: 122-124.
10. Elnara Marcia Negri, Bruna Piloto, Luciana Kato Morinaga, et al. Heparin therapy improving hypoxia in covid-19 patients : A Case series. Med Rxiv, Cold Spring Harbor Laboratory Press, 2020;15.20067017.
11. Chen Shi, Cong Wang, Hanxiang Wang, et al. The potential of low molecular weight heparin to mitigate cytokine storm in severe COVID-19 Patients: A Retrospective cohort study. Clin Transl Sci. 2020.
12. Jecko Thachil, Ning Tang, Satoshi Gando, et al. Type and dose of heparin in covid-19: Reply. J Thromb Haemost. 2020; 18; 2063–2064.

13. van Haren, Frank M P, Page Clive, et al. Nebulised heparin as a treatment for covid-19: Scientific rationale and a call for randomised evidence. Critical Care (London, England), BioMed Central. 2020; 4: 454

14. Jianshe Lang, Ning Yang, Jiejie Deng, et al. Inhibition of SARS pseudovirus cell entry by lactoferrin binding to heparan sulfate proteoglycans. PloS One. 2011; 6: e23710

15. Courtney Mycroft-West, Dunhao Su, Stefano Elli, et al. The 2019 Coronavirus (SARS-CoV-2) surface protein (spike) s1 receptor binding domain undergoes conformational change upon heparin binding. 2020; 29: 971093.

16. Conzelmann C, Muller JA, Perkhofer L, et al. Inhaled and systemic heparin as a repurposed direct antiviral drug for prevention and treatment of covid-19. Clin Med (Lond). 2020; 30: 2020-0351

17. Kim SY, Jin W, Sood Aukuj, et al. Glycosaminoglycan binding motif at s1/s2 proteolytic cleavage site on spike glycoprotein may facilitate novel coronavirus (sars-cov-2) host cell entry. BioRxiv, Cold Spring Harbor Laboratory. 2020; 14: 041459.

***Correspondence to:**
Antonio Pisani
Department of Public Health,
University of Naples
"Federico II", 80131 Naples, Italy
E-mail: antonio.pisani13@gmail.com