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Research Article

The Proposed Dual Clinical Benefits of Continuous Heparin Infusion as Red Blood Cell Invasion Inhibitor and as an Anticoagulant in Management of Complicated SARS-Cov-2 Infection

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Abstract: Now, Enveloped positive single stranded RNA-coronavirus is considered the most world concern. The discovery of the new pathogenesis of SARS-COV-2 is requiring us to think out of the box in order to manage this pandemic outrageous virus that has took many lives and still does. Up to this date, 18th of April, 2,256,844 coronavirus confirmed cases and around 154,350 deaths all over countries and territories. General clinical presentation of the infection includes fever, dry cough and shortness of breath and may develop to acute respiratory distress syndrome ARDS, pneumonia, sepsis multi-organ failure, respiratory arrest and eventually causing death. COVID-19 is more likely to affect elderly with comorbidities, requiring ICU admission and mechanical ventilation. Therefore, finding novel treatment approaches is of crucial importance. Disseminated intravascular Coagulation (DIC) is a common complication in hospitalized patients especially ICU patients. Recently, coronavirus was observed to attack heme on the 1-beta chain causing iron-porphyrin dissociation. Heparin pleiotropic effects of anticoagulation and RBC protective effect, makes it a drug of choice in management of COVID-19. It is reported in literature that heparin and heparin like compounds due to polysaccharide component have high inhibitory effects on microbial invasion of red blood cells RBC. The dual benefit of heparin can be of significant importance in COVID-19 and especially for complicated cases and most susceptible individuals.

Keywords: Anticoagulant; COVID-19 Infection; Disseminated Intravascular Coagulation; Unfractionated Heparin; RBC invasion inhibitor.

INTRODUCTION

Globally COVID-19 fatal cases and deaths are directly linked to the cytokine rush and the acute respiratory distress syndrome (ARDS), this is partially right because the full scenario behind the pathogenesis of COVID-19 has not been widely discussed, it is not just a virus that attack the respiratory system, but also many other organs and systems are involved such as kidney, genitourinary tract especially in males, gastrointestinal tract, liver, cardiovascular system and circulatory system (including endothelium) due to the high expression of ACE-2 receptors (a transmembrane protein which has two sides and presents at the surface of different cells) in some of these tissues as it is the binding domain of COVID-19 via its spike glycoproteins.(Cai, 2020),(Fan, Li, Ding, Lu, & Wang, 2020),(Guo, Huang, Lin, & Lv, 2020). As the symptoms of COVID-19 include gastrointestinal system as diarrhea, vomiting , abdominal pain, lack of appetite and increase in both liver enzymes ALT and AST, also patients will appear with fever and respiratory symptoms as dry cough and dyspnea, all of these symptoms are visible, easily detected and managed and don't necessarily lead to death(Pan et al., n.d.), (Sohrabi et al., 2020), but what has the characteristic of fatality and puts the patients on the edge of death is the involvement of the circulatory system and its role in the prognosis of the disease. As a result of the circulatory system involvement the patients have suffered from pulmonary embolisms, thrombosis and high blood pressure due to the insult of the endothelial layer, also the virus has succeeded to cause several dysfunctions in the endothelium which resulted in the findings of disseminated intravascular coagulopathy (DIC) in non-survivors.(Sardu, Gambardella, & Morelli, 2020).

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Mast cells and basophiles synthesize glycosaminoglycan which is called heparin a heterogeneous mixture of branched glycosaminoglycans, was discovered as an anticoagulant by McLean in 1916. It requires a plasma cofactor which is now known as antithrombin for its anticoagulant activity, It also binds to heparin cofactor II and platelets. Heparin and its derivative, LMWH, are widely administrated in low doses for primary prevention of VTE. The preferred route for UFH administration is continuous intravenous (iv.) infusion or subcutaneous (sc.) injection. Heparin in a fixed low dose: 5000 IU as sc. injection every 8 to 12 h resulted in 60–70% risk reduction of VTE and fatal PE events. (Izadpanah et al., 2015) . Coronavirus reported of having the ability to bind the porphyrin due to having surface glycoproteins and transcribed non-structural protein ORF8. At the same time other non-structural proteins including ORF1ab, ORF10 and ORF3a have the ability to attack the heme. Heparin may have the ability to inhibit the coronavirus heme binding and thus, prevent complications resulting from increased serum levels of free iron and lowered capacity of RBC of oxygen carrying ability. In this review we propose the use of unfractionated heparin in the treatment of the hypercoagulability status in critically infected SARS-COV-2 patients due to many reasons.

DISCUSSION

In terms of biochemical laboratory tests , a recent study observed biochemical examination of 99 coronavirus patients with pneumonia have; decreased levels of neutrophil and lymphocyte counts, significantly increased levels of ferritin, erythrocyte sedimentation rate, and C reactive protein. Function hemoglobin decreases, serum ferritin and heme increase, high free iron damages the tissue and increase the inflammatory state of the patient. This is the general clinical features of COVID-9 patients. A relation between coronavirus and RBC invasion lead us to find treatment approaches targeting this relation.

Physiologically, Heme is a porphyrin containing iron and it is an important part of hemoglobin. Hemoglobin has the oxygen carrying ability. Oxygen and carbon dioxide exchange occurs at the cellular level because of hemoglobin, interference with heme normal metabolism pathway by coronavirus results in gas exchange disruption causing hypoxia and further complicating the condition. Respiratory infection complicated with hypoxia increases the mortality risk in COVID-19 patients. Red blood cell invasion by coronavirus requires protein-protein interaction, intracellular signals protease cleavage events and several coordinated steps all occurring in blood, this makes the whole invasion process directly targeted and exposed by drugs. Attachment, receptor binding and fusion are the three steps of viral cellular invasion.

Heparin is one of the oldest drugs, it is a known RBC invasion inhibitor, a distinctive structure of polyanionic polysaccharides that has an anticoagulant activity, this linear carbohydrate polymer consists of both glucosamine and pyranosyluronic acid, its heavy negative charge due to the presence of carboxylic acids and sulfo-groups. Heparin doesn't undergo tertiary and quaternary folding, leaving it as a planer helical protein that undergoes different protein-protein interactions and many other biological interactions. The major force that contributes in heparin-protein interactions is ionic bond (strong bond), also hydrogen and hydrophobic bonds which makes the dissociation of this complex hard. Highly sulfated heparin was observed to have inhibitory effects on RBC parasite invasion. This made it a new target as anti-malaria parasite RBC invasion. Sulfated carbohydrates were observed to inhibit attachment to RBC the initial step in invasion. In a clinical trial to test the binding domains of various proteins and heparin it was found that heparin binds with different viral envelop glycoproteins such as herpes simplex virus (HSV) glycoproteins Gb, Gc and Gd therefore inhibits viral entry and infusion, another example is binding of heparin to HIV-1 glycoprotein 120 which will also inhibit viral entry by block the viral attachment . In addition to its potential role in inhibiting COVID-19 viral entry to RBCs (Oncley, Ellenbogen, Gitlin, & Gurd, 1952). The use of heparin and glycosaminoglycan is also an appropriate candidate in viral vaccine development.

The anti-inflammatory properties of UFH make it as a better option in some conditions such as asthma, ulcerative colitis and burns. Some animal studies show heparin has protection effect against ischemia-reperfusion injury (characterized by infraction of cells, blood thrombosis, endothelium dysfunction and micro-vascular collapse) where neutrophils play a leading role in this damage as they release proteases and oxidants that necrotize the cells, so administration of heparin before the reperfusion has shown a clinical benefit in decreasing the complications . It is also noteworthy that heparin has a role in inhibiting leukocytes adhesion that lead to intravascular

aggregations, although it has an inhibitory role for cytokines it inhibits the proteolytic degradation of interferon gamma (which is involved in COVID-19 eradication) thus reduce its clearance.(Young, 2008). Many animal trials have shown the direct effect of heparin in reducing TNF-alpha and impairs its migration to T-cells, IL-6 and an increase in IL-10 (anti-inflammatory mediator), as a result of inhibiting the pro-inflammatory mediators this can enhance the immunity to eradicate the virus by restoring the balance and rid of damaging components.(Elsayed & Becker, 2003).

Covid-19 was observed to cause decrease in T-cell lymphocyte counts, hyper-inflammatory status, cytokine storm and series of severe immune responses. Also, complicating the viral infection with coagulopathy and leading to poor prognosis. Infection induces endothelial cell dysfunction and thrombin produced excessively and leading to hyper-coagulability status. In addition, severe pneumonia and hypoxia stimulate thrombosis through increased blood viscosity and hypoxia-inducible transcription factor-dependent signaling pathway. Severe COVID-19 patient clinical and laboratory findings were hypoxemia one week after infection onset and D-dimer elevation so to decrease the viral effect on hemoglobin and risk for coagulopathy , a supportive and pharmacological treatment of choice is a low dose anticoagulation of unfractionated heparin was suggested in a study published on March, 2020. (Thachil, 2020).

Why our choice is heparin (unfractionated heparin) rather than low molecular weight heparin (LMWH) , a fair comparison should be conducted, first regarding to the molecular weight, heparin has an average molecular weight of 15,000kDa while low molecular weight heparin has an average molecular weight ranges from 4000-6500kDa, the anticoagulant effect of heparin is seen by its high affinity toward antithrombin-3 via its pentasccharides, therefore the antithrombin-3 produce an inactivation of factors 10a, thrombin (factor 2), and factor 9a. in comparison as LMWH is a degraded form of heparin, therefore reduced its ability to bind thrombin and inactivate it, but its activity against factor 10a hasn't changed, also it shows a lower affinity to bind plasma proteins, macrophages, platelets, vascular matrix proteins and endothelial cells. Due to these reasons the selection of heparin rather than LMWH due to its mechanism is reasonable, because heparin would exhibit a better anti-inflammatory action (lmwh, n.d.),(Hirsh, Anand, Halperin, & Fuster, 2001). Moving to the comparison between the pharmacokinetic properties of both anticoagulants, it is true that LMWH as enoxaparin, tinzaparin and dalteparin have more predicted pharmacokinetic profile, the bioavailability of LMWH when administered subcutaneously is better than heparin, administering LMWH doesn't require laboratory monitoring except of some cases as renal failure, pregnancy and either low body weight < 45kg or high body weight >120 kg. While administering heparin requires aPPT monitoring. Moreover, when severe bleeding occurs the use of protamine sulfate and it is more effective in reversing the effect of heparin rather than LMWH (OBJECTIVE, 2013). A clinical trial has shown that major risk of hemorrhagic bleeding of LMWH in comparison with Heparin, and the length of hospital stay is higher with heparin compared to LMWH (Levine et al., 1996).

Lastly, it is important to mention the half-lives of these two anticoagulants, LMWH reach a peak plasma concentration after 2- 4 hours of SQ administration with an average half-life of 3-4 hours("Low Molecular Weight Heparin - an overview | ScienceDirect Topics," n.d.), while unfractionated heparin half-life ranges from 30-90minutes.("A Review of Unfractionated Heparin and Its Monitoring," n.d.). Relaying on the half-lives of these agents, it is safer to administer Heparin in a continuous infusion at treatment dose due to its short half-life which allows the flexibility to terminate or increase its dose according to laboratory measurements and patients therapeutics outcomes, when used for DIC in COVID-19 patients.

Up-to-date, there is no officially approved antiviral treatment or vaccination for COVID-19. This force us to use already existing treatments to slow down the pandemic SARS-CoV-2 infection spreading. Last, at this point, combining the effects of RBC invasion inhibitory and anti-thrombosis can be beneficial in COVID-19 patients. According to literature we can conclude that Heparin use is promising in deceasing mortality rate of these patients and improving the clinical outcomes.

CONCLUSION

It is a terrible fact that COVID-19 is still spreading to thousands and thousands of the world population. COVID-19 patients should be monitored and prophylactically treated with anti-coagulant heparin to reduce the mortality that results from fatal DIC, so the suggestion of Heparin due to its versatile

aforementioned uses is significantly has positive impact of COVID-19 patients outcomes. Also it is fair to say that unfractionated heparin is considered an affordable agent even by countries with limited resources, although it is hard to affirm all of these benefits without conducting a clinical trial to see the outcomes of such agent, as it is worthy to try our best to rescue patients with critical cases of COVID-19 who are on the edge of death due to DIC.

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