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A review on Heparin as a therapy for COVID-19 patients and increase the patient's survival.

Vishva Nanthakumar[1], Jency Cesilraj[2]

[1]Doctor of Pharmacy. Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnan Koil, Srivilliputhur, Viruthunagar, Tamilnadu – 626126, India
[2]Doctor of Pharmacy, Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnan Koil, Srivilliputhur, Viruthunagar, Tamilnadu – 626126, India

ABSTRACT

Aim: The impact of the coronavirus disease 2019 (COVID-19), caused by the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is rapidly spreading globally. We are seeking to provide a top-level view of the data supporting the therapeutic use of heparin and low molecular weight, as an anticoagulant for the treatment of SARS-CoV infection.

Materials and Methods: In this article, we literally show evidence from various clinical trials, experimental data, and other analyses to stimulate the importance and future research on heparin as a therapy for covid.

Conclusion: Recent evidence reports that the use of heparin reduces mortality in patients with severe coronavirus with coagulopathy. Several biochemical studies show strong binding of heparin and heparin-suchlike molecules to the Spike protein, which results in the inhibition of the virus to enter the cells and the evidence for the role as an anti-inflammatory and modulating the cytokine stormleads to necrosis. Additionally, we review clinical evidence establishing the adoption of heparin as a therapy in COVID-19 increasing the survival of patients. The furnished information suggests that heparin can be employed in the treatment protocol for COVID-19.

Keyword: COVID-19, Heparin, Anticoagulation, Antiviral, Anti-inflammatory, Mortality

INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by a coronavirus (SARS-CoV) that causes a severe acute respiratory syndrome,[1] a characteristic hyperinflammatory response,[2] vascular damage,[3] microangiopathy,[4] angiogenesis,[5] and widespread thrombosis.[6] Four stages are recognized at COVID-19: the initial stage is distinguished by upper respiratory tract infection; the second by the onset of dyspnoea and pneumonia; the third by a worsening clinical scenario dominated by a cytokine storm and the resulting hyperinflammatory state; and the fourth by death or recovery.[7,8] At present, protocols developed in specialized centers have included the use of chloroquine and hydroxychloroquine & anti-inflammatory agents such as tocilizumab and dexamethasone with promising results[9] and remdesivir, the latter with promising results. anti-virals such as lopinavir/ritonavir with negative results, and The use of Anticoagulants which increases the survival of COVID-19 severity patients.[10] Finally, recent evidence indicates that heparin may be a promising candidate for COVID-19 antiviraltherapy.[11,12]

This review will focus on (A) Anticoagulation in COVID-19. (B) Heparin/LMWH as an Entry inhibitor. (C) heparin as anti-inflammatory (D) Neutralisation of chemokines & cytokines.

MECHANISM OF HEPARIN IN COVID-19

1. Prevention of infection by decreasing viral entry. Heparan sulfate, heparin & Low molecular weight heparin have been shown to interact with SARS-CoV-2 spike glycoprotein.
2. Heparin & Low molecular weight heparin has been shown to inhibit heparan activity, which is increased in COVID-19 and associated with disease severity.
3. Reduction of Interleukin-6 release associated with cytokine storm. Heparin & Low molecular weight heparin interact with chemokines, and cytokines, including those produced in the 'cytokine storm' in COVID-19.

4. Interference with leukocyte trafficking. Heparin & Low molecular weight heparin neutralization of chemokine and cytokines may impact leukocyte recruitment and trafficking to sites of inflammation and also like neutralization of chemokine, and cytokines.
5.Heparin & Low molecular weight heparin promotes anticoagulation via anti-thrombin III binding.
6. Prevention and treatment of thrombosis of small and middle-size vessels leading to lung failure.

ANTICOAGULANT THERAPY OF HEPARIN

Heparin is heterogeneous of unbranched polysaccharide chains belonging to the glycosaminoglycan found in the secretory granules of the mast cell. It is the polymer of alternating D-glucuronic acid and N-acetyl-D-glucosamine residue.[13] Heparin is firstly bound to the inactivated antithrombin to get activated. The sulfated nature of its constituent HS glycosaminoglycan chains confers heparin with the highest negative charge density as compared to other biomolecules.[14] This charge allows heparin to strongly interact with an immense number of proteins & enhance the inhibitory activity of the plasma protein antithrombin against several serine proteases of the coagulation system that provide anticoagulant activity.[15] Heparin is mostly known for its anticoagulant properties, so commercial forms of heparin include unfractionated heparin (UFH) and low molecular weight heparin.[16,17]

Unfractionated heparin is composed of HS chains that is >30 saccharide in length whereas low-molecular-weight heparin has ≤ 22 saccharides.[18]

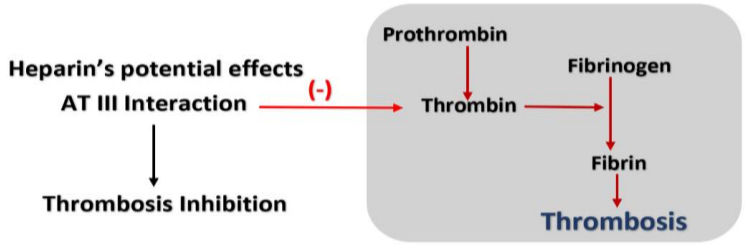

Fig.1 Schematically represents the mechanism of Heparin's anticoagulant property

Patients with COVID-19 are at a high risk of venous thromboembolism despite the use of thromboprophylaxis.[19]There has been a suggestion that the use of Anticoagulation reduced venous thromboembolism rate and mortality.[20]

Clinical observation of heparin as an anticoagulant

Patients with COVID-19 are at a high risk of venous thromboembolism despite the use of thromboprophylaxis.[21] In a recent Chinese study by Wuhan, 449 patients with severe COVID-19 were analyzed regarding the benefits of Anticoagulation prophylactic, and therapeutic.[22,16,23] By using different increasing D-dimer cutoffs, the mortality improved steadily in patients who received anticoagulation, compared to those who did not receive anticoagulation. It is worth noting that the patients received both prophylactic and therapeutic doses of enoxaparin and apixaban for the first 48 hours of hospitalization. Within 48hrs of admission,most patients had drawn D-dimer levels(69.7%). The choice of AC varied within the D-dimer level. Transfusion requirement for treatment: apixaban prophylaxis (OR - 0.46, $p = 0.34$), apixaban therapy (OR 0.79, $p = 0.51$), and enoxaparin prophylaxis (OR-0.68, $p = 0.31$) were all associated with a significant decrease in mortality. It showed several differences in Death between prophylactic [1 Death in 8 patients] and therapeutic [2 deaths in 18 patients].[24] The median days of anticoagulants were 3 days and a longer course of anticoagulants correlated with improved survival.[25]

According to a study by Italy, out of 2,574 COVID-19 patients, 70.1% received heparin. LMWH of 99.5% was the most used formulation. Death rates for cases receiving heparin or not were 7.4 and 14.0 per 1,000 person-days, individually. After adjustment for propensity scores, the study found a 40% lower risk of death in patients receiving heparin. Finally, heparin treatment was associated with lower mortality, particularly in severely ill COVID-19 patients and in those with strong coagulation activation.[26]

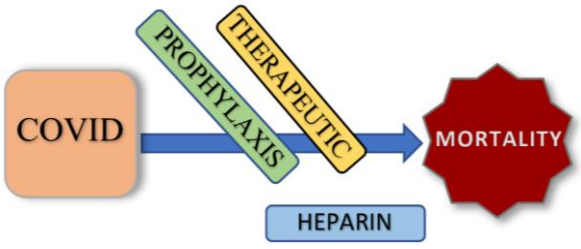

Fig.2 Representation of Heparin treatment decrease mortality.

HEPARIN/LMWH AS ANTIVIRAL

The SARS-CoV spike glycoprotein (SGP) binds to glycosaminoglycans like heparan sulfate, which is found on the surface of virtually all mammalian cells.[27,28] The ACE2 receptor is needed for viral entry but it is not the primary binding site on the cell surface.[29,30] The heparan sulfate proteoglycans function as adhesion molecules for interaction between COVID Virus and its receptor.[31] Heparin may bind the SARS-CoV-2 spike protein[32] and function as a competitive inhibitor for viral entry, thus decreasing infectivity. Interestingly, shorter-length heparins, similar to those that begin in therapeutic low-molecular-weight heparin, didn't appreciably bind the spike protein.[33] The soluble form of heparin inhibits the herpes simplex virus from binding to cell surface HS in a cell-based assay[34]& the Elimination of cell-surface HS by the addition of exogenous heparin reduced the ability of the virus to bind to the cell surface and increased cellular resistance to infection.[35}

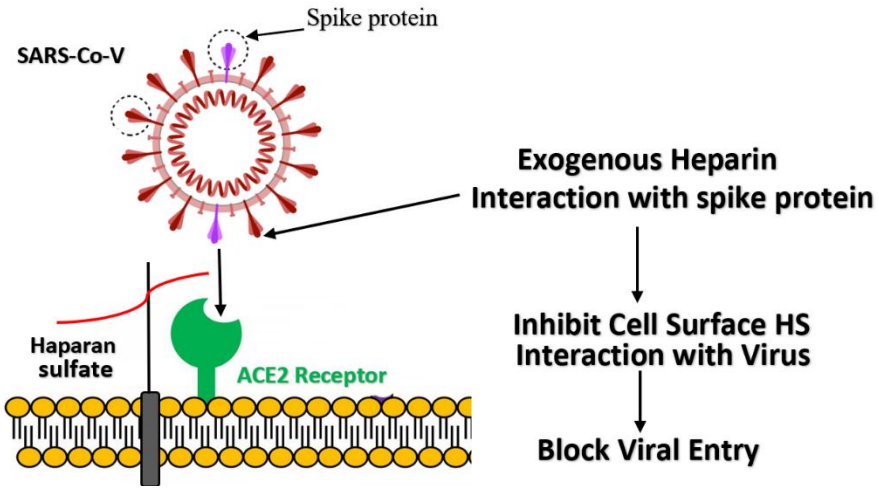

Fig.3 Representation of SAR-Co-Viral entry is inhibited by Heparin.

Coronavirus (SARS-CoV) induces endothelial dysfunction and loss of endothelial barrier function. Low molecular weight heparins serve as an inhibitor of heparan.[36]

Preclinical evidence for an antiviral effect of heparin

Heparin isan antiviralfor human immunodeficiency virus (HIV) infection. At a concentration of 7.5 μg/mL, heparin showed a 50% reduction in HIV-induced cytopathogenicity to MT-4 cells. To further clarify the beginning mechanism, the same group illustrated that heparin can not directly neutralize HIV but can prevent the adhesion of HIV to MT-4 cells. The inhibitory effect of fragmented heparin with various MWs ranging from 1400 to 11,000 was further examined.[37]

Clinical application of heparin as antiviral therapy

To test the antiviral activity, a study of 58 individuals, 10 healthy and 48 COVID-19 positives, showed that plasma heparan activity was significantly elevated in COVID-19 patients, and in addition, heparan activity was associated with disease severity. The use of LMWH serves as an inhibitor of heparan activity.[38,39]

Existing evidence suggests that heparin treatment might reduce the binding of viral spike protein to cell surface HS proteoglycan, thereby inhibiting initial infection or spreading from infected to noninfected cells.

HEPARIN AS AN ANTI-INFLAMMATORY

Heparin also involves anti-inflammatory effects as it can modulate the function and activity of mediators of the immune response.[40]Certainproteins activity acting as mediators of inflammation, including CD11b/CD18, eosinophil cationic protein, IL-8, neutrophil elastase, major basic protein, P- and L-selectin, platelet growth factor 4, and stromal-derived factor 1a is modulated by heparin.[18]

The anti-inflammatory effects of heparin and heparan sulfate glycosaminoglycan fragments involve two general mechanisms: 1) dampening of inflammation through interaction with proinflammatory proteins and 2) preventing adhesion and an invasion of inflammatory cells to a diseased area.[41] Heparin interferes with both complement pathways, the classical and alternative pathways, by binding to and inhibiting the formation of several complement factors (e.g., active C1 complex, C3 convertase).[42]

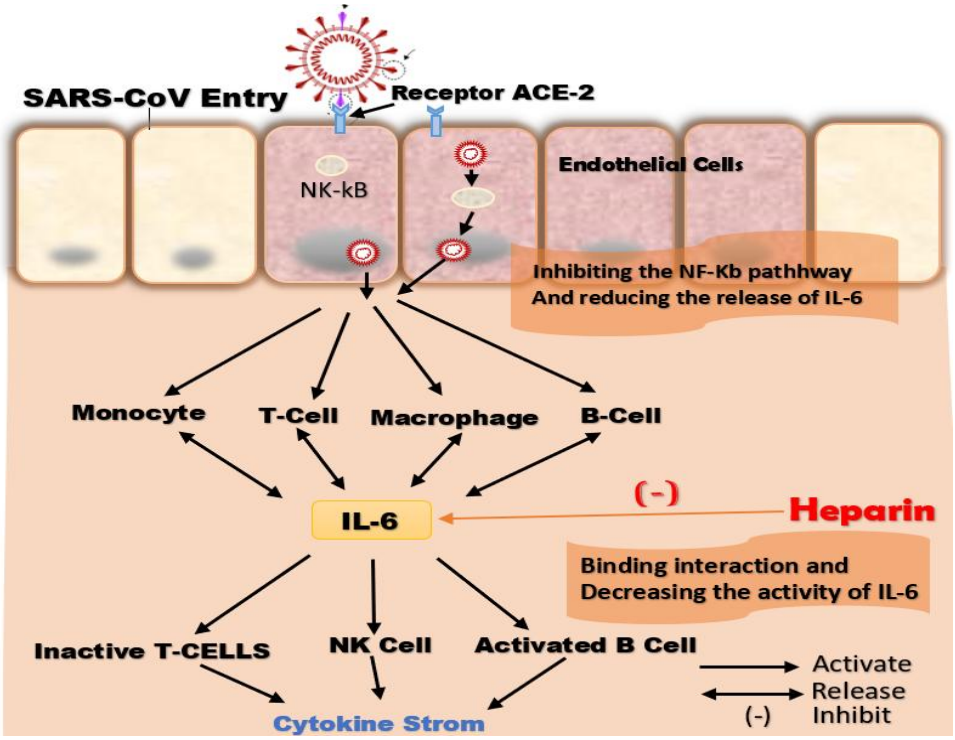

Fig.4 Schematically represents the Anti-inflammatory action of heparin.

Neutralisation of chemokines & cytokines

During the evolution, if SAR-CoV infection, the development of cytokines storm leads to necrosis of epithelial cells, and increased permeability of vascular cells leads to cell death.[44] Heparin can interact with pro-inflammatory cytokines and chemokines,[45] preventing these pro-inflammatory molecules from interacting with their specific receptors. Low molecular weight heparin inhibits neutrophil adhesion to activated endothelial cells by binding to P-selectin.[45] In addition, heparin can bind P/L-selectin,[46] which is involved in adhesion between leukocytes and endothelial walls. Heparin also interacts with integrin adhesion molecules, inhibiting the activation and tight adhesion of leukocytes to the endothelium.[47] Heparin inhibits neutrophil chemotaxis and leukocyte migration during inflammation.[48]

Anti-inflammatory effects of heparin
↓ NF-κB activation
↓ Chemokine
↓ Cytokine
↑ Interaction with the complement system
↓ P- and L-selectin activity
↓ Leukocyte migration
↓ Neutrophil chemotactic factors

Clinical observation of heparin as an anti-inflammatory

For the clinical observation, patients were divided into heparin and a control group based on whether low molecular weight heparin (LMWH) was used. D-dimer, C-reactive protein, peripheral blood lymphocyte percentage, interleukin-6, and other indices in 42 patients with novel coronavirus pneumonia were retrospectively analyzed to compare and evaluate the progress of patients before and after LMWH treatment.[43]

The results show that the anti-inflammatory effects of LMWH are associated with the reduction of IL-6 levels in COVID-19 patients.

CONCLUSION

On the whole, heparin is employed in various thrombotic diseases. Heparin still possesses beneficial effects in the treatment of COVID-19. The risk factors and other beneficial effects including antiviral and anti-inflammatory property is still to be considered. But the anticoagulation property of heparin in COVID-19 treatment should be fully recognized.

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