

The Benefits of Heparin Use in COVID-19: Pleiotropic Antiviral Activity beyond Anticoagulant and Anti-Inflammatory Properties

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Coronavirus disease 2019 (COVID-19), a life-threatening infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is causing the worst pandemic outbreak since the Spanish flu of 1918–1919.¹

Several lines of evidence now suggest that COVID-19 is a prothrombotic disorder, in that SARS-CoV-2 infection may trigger activation of primary and secondary hemostasis, along with inhibition of fibrinolysis, by a kaleidoscope of mechanisms, including direct and indirect platelet activation,² derangement of the von Willebrand factor/ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, 13) axis,³ endothelial cells infection/activation/injury,⁴ monocytes and/or macrophages infection/activation with subsequent release of prothrombotic substances (namely tissue factor),⁵ onset of antiphospholipid antibodies,^{6,7} increased lipoprotein (a),⁸ overactivation of the complement system,⁹ combined with a “shutdown” (or at least a substantive reduction) of fibrinolysis.¹⁰

Due to this prothrombotic state, anticoagulant therapy is recommended, and for which heparin therapy has now become routine practice for hospitalized patients with COVID-19.¹¹ This approach is aimed to mitigate the magnified risk of in situ pulmonary thrombosis,¹² venous thromboembolism,¹³ arterial thrombosis,¹⁴ as well as disseminated intravascular

coagulation.¹⁵ According to the Scientific and Standardization Committee Communication of the International Society of Thrombosis and Haemostasis, routine thromboprophylaxis with standard-dose unfractionated heparin (UFH) or preferably with low molecular weight heparin (LMWH) should be administered after assessment of bleeding risk in all non-intensive care unit (ICU) hospitalized patients with SARS-CoV-2 infection, while routine use of a prophylactic dose of LMWH (or UFH) should be administered to all ICU hospitalized COVID-19 patients.¹⁶ Similar recommendations have been endorsed by many other associations, organizations, and expert groups all round the world,¹⁷ thus essentially becoming the standard of care.

Emerging evidence now suggests that heparin, representing a historically “antique” anticoagulant drug, may also generate intriguing pleiotropic effects beyond its antithrombotic activity or potential. Notably, the spike protein of SARS-CoV-2 perhaps represents the major determinant of virulence and infectivity since it mediates, through its receptor-binding domain (RBD) within the S1 domain, the interaction of SARS-CoV-2 with host cells receptors (especially with the angiotensin-converting enzyme; ACE2) and then the fusion, through its S2 domain, between viral envelope and the host cell membrane.¹⁸ Several attachment cofactors have been implicated in the binding

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between SARS-CoV-2 and host cell receptors (e.g., ACE2), including phosphatidylserine receptor, neuropilin-1, CD147, C-type lectins, and heparan sulfate proteoglycans.¹⁹

Of particular relevance, it has been previously demonstrated that the binding of SARS-CoV-2 to human cells may be facilitated by heparan sulfate, which has thus been proposed as an important cofactor for virus penetration in host cell, since pretreatment with heparinase reduces significantly the binding of the SARS-CoV-2 spike protein with the ACE2 host cell receptor.²⁰ Electron micrograph studies revealed that such a potential mechanism is mediated by a heparan-dependent enhancement of open conformation of the RBD, which would hence increase its affinity to ACE2. This heparan sulfate-mediated pathway was found to be especially heightened in SARS-CoV-2 variants bearing the G614 polymorphism in the spike protein,²¹ a mutation that has now become almost commonplace in all identified lineages worldwide. In keeping with these findings, it was also found that bacterial modification of heparan sulfate at the surface of host cells was associated with substantial changes of SARS-CoV-2 infectivity.²² It is therefore not surprising that other authors reported that blocking O-glycan and especially N-glycan biosynthesis at the host cell surface dramatically decreased SARS-CoV-2 penetration into ACE2-expressing cells,²³ thus confirming the key role played by heparinoids in mediating virus-cell interaction and host cell penetration.

In a more recent study, published by Paiardi et al.,²⁴ the authors found that heparin actively binds to SARS-CoV-2 spike glycoprotein, and this linkage inhibits host cell infection by at least three separate mechanisms, involving (1) allosteric inhibition of the binding to host cell receptors (binding and allosterically impairing the hinge region of the RBD), (2) direct competition with spike for binding to heparan sulfate proteoglycan coreceptors, and (3) prevention of furin-mediated cleavage of the spike proteins (making unavailable the spike S1/S2 cleavage site), which is a major determinant of SARS-CoV-2 virulence and pathogenicity.²⁵

The consolidated evidence that SARS-CoV-2 is thus efficiently able to interplay with heparan sulfate proteoglycans on host cell surface for primary attachment before high-affinity

interaction of RBD with ACE2,²⁶ provides reasonable and reinforced support for the importance of heparin usage in COVID-19.²⁷ In fact, the antiviral activity of heparin may ultimately complement its well-known anticoagulant and even anti-inflammatory properties (→Fig. 1),²⁸ thus generating an additional (pleiotropic) effect—besides lowering the risk of thrombosis and counteracting hyperinflammation—that may favorably influence the clinical course of SARS-CoV-2 infection, especially in the most vulnerable subjects. Notably, nasal heparin sprays are undergoing clinical trials to evaluate their potential to mitigate SARS-CoV-2 infectivity,²⁹ and thus aid other approaches to prevent COVID-19, including vaccination efforts.

Conflict of Interest

None declared.

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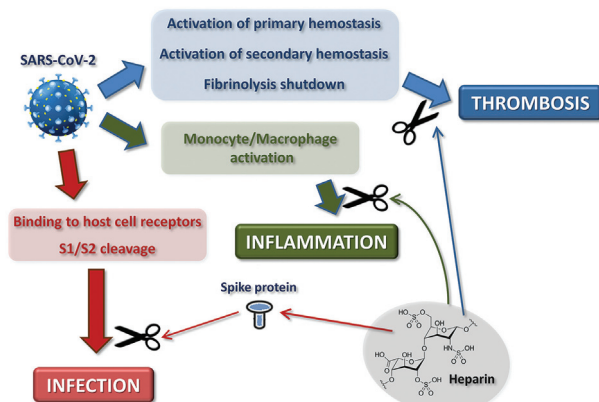


Fig. 1 Postulated pleiotropic activities of heparin in coronavirus disease 2019 (COVID-19).

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