MINI-REVIEW

Heparin as a therapy for COVID-19: current evidence and future possibilities

Joseph A. Hippensteel, Wells B. LaRiviere, James F. Colbert, Christophe J. Langouët-Astrié, and Eric P. Schmidt

1Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado; 2Division of Infectious Diseases, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado; 3Medical Scientist Training Program, University of Colorado Anschutz Medical Campus, Aurora, Colorado; and 4Department of Medicine, Denver Health Medical Center, Denver, Colorado

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INTRODUCTION

Coronavirus 2019 (COVID-19), the disease associated with infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 (50) and is now the most significant worldwide public health crisis since the influenza pandemic of 1918. Despite this immense global burden, no pharmacologic therapies have proven definitively beneficial (25). On the basis of our clinical experience in intensive care units in Colorado and those shared by the wider critical care community, we conclude that many therapies are being administered despite limited evidence. Anticoagulants that have been utilized widely are unfractionated (full-length) heparin and low-molecular weight heparins. For the purposes of this review, heparin herein refers to both unfractionated and low-molecular weight variants, unless otherwise designated.

In this review, we discuss the pathophysiologic rationale and current evidence for the use of full-dose heparin (i.e., therapeutic rather than prophylactic dosing) as an anticoagulant in COVID-19. We also discuss a subset of non-anticoagulant effects of heparin that may prove beneficial for the treatment of COVID-19. Finally, we discuss potential risks associated with the implementation of heparin for the treatment of SARS-CoV-2, including but not limited to bleeding and immune-mediated heparin-induced thrombocytopenia (HIT).

HEPARIN STRUCTURE AND FUNCTION

Heparin is a heterogeneous preparation of long, linear highly sulfated heparan sulfate (HS) glycosaminoglycans purified from porcine intestines (see Fig. 1). The sulfated nature of its constituent HS glycosaminoglycan chains confers heparin with the highest negative charge density of any known biomolecule (43). This charge allows heparin to strongly and selectively interact with an immense number of proteins, the most classic being its interaction with serine protease inhibitor antithrombin-III (AT3) that provides its anticoagulant activity. This anticoagulant activity is dependent on the presence of a precise pentasaccharide sequence within longer HS chains that allows for AT3 binding as shown in Fig. 1. Beyond AT3, hundreds of
Fig. 1. Structure and function of heparin. Heparins are a heterogeneous mix of heparan sulfate (HS) glycosaminoglycans. Each HS strand is composed of repeating disaccharide units of N-acetylgalactosamine (GlcNAc) and glucuronic acid (GlcA) or iduronic acid (IdoA). GlcNAc can be sulfated at three distinct sites (-6S, -NS, and -3S) and IdoA at one (-2S). Unfractionated heparin is composed of HS chains that are >30 saccharides in length, whereas low-molecular weight heparin constituent HS chains are 22 saccharides or less (3). The charge distribution of heparin imparted by the presence of the precise pentasaccharide sequence shown allows for the binding of heparin to serine protease inhibitor antithrombin-III (AT3), conferring its primary anticoagulant effect. Innumerable other sulfation sequences are found in heparin preparations, which leads to binding and biologically relevant activity modulation of many other proteins.

Biologically relevant, heparin-protein interactions have been described, which has led to the recognition of an immense number of potential off-target (both positive and negative) effects of heparin of unknown clinical importance.

COAGULOPATHY AND THROMBOSIS IN COVID-19

Many patients with COVID-19 develop a clinically significant coagulopathy (7, 32). The coagulopathy associated with COVID-19 is characterized by thrombocytopenia, minor prolongation of prothrombin time (PT) and partial thromboplastin time (aPTT), and elevated serum D-dimer and fibrinogen, consistent with a consumptive coagulopathy (7). This profile is compatible with postmortem examinations of patients with COVID-19 describing severe endothelial injury, microangiopathy, and alveolar capillary microthrombi (2). Endotheliitis directly elicited by SARS-CoV-2 may be the pathophysiologic link to these postmortem findings (39).

In addition to laboratory and histopathological evidence of disordered coagulation and endothelial injury, several reports suggest that patients with COVID-19 are at high risk for developing clinically significant large-vessel thrombosis. Early anecdotal evidence of venous thromboembolism (VTE) in critically ill patients has been confirmed by multiple case series describing high rates of VTE in COVID-19, with incidence estimates ranging between 8% and 54% (18, 22), significantly exceeding those reported in critically ill patients with H1N1 influenza of 2% (36) and sepsis of 5% (30). Reports of large-vessel strokes in patients, including those younger than 50 yr, infected with SARS-CoV-2 also suggest hypercoagulability (28). Concordantly, a postmortem study of 12 patients positive for COVID-19 found thrombosis in 58% of cases, which was found to be responsible for 25% of deaths (45).

Taken together, it is likely that COVID-19-associated coagulopathy and thromboses contribute to the morbidity and mortality of the disease. However, it is important to recognize that other non-COVID-19 critical illnesses have demonstrated similar evidence of coagulopathy, yet failed to benefit from anticoagulation treatment in randomized controlled studies. For example, coagulopathy has been widely recognized as a contributor to organ failure in sepsis, a disease characterized by circulating D-dimer concentrations that approximate levels observed in patients with COVID-19 (Fig. 2; 10, 32, 38, 40). However, studies that have targeted this coagulopathy in sepsis with thrombomodulin (40), AT3 (42), tissue factor pathway inhibitor (1), and activated protein C (31) have all failed to improve mortality, despite improving laboratory indexes of coagulopathy. These studies suggest that coagulopathy may simply be a consequence of sepsis, as opposed to a key pathogenic driver of disease. Alternatively, as discussed below, coagulation may impart both harmful and protective effects within the injured lung, negating any clinical benefit (or harm) from anticoagulant therapy.

![Heparin in COVID-19](image)

Fig. 2. Coagulopathy in sepsis compared with coronavirus disease 2019 (COVID-19). Circulating levels of D-dimer, a marker of coagulopathy, have been found to be significantly and similarly elevated in sepsis and COVID-19. This panel represents medians and interquartile range. Studies: Bernard et al. (10), Vincent et al. (40), Tang et al. (38), and Richardson et al. (32). NYC, New York City; pts, patients; RCT, randomized controlled trial.
HEPARIN AS AN ANTICOAGULANT IN COVID-19

Previous failures of anticoagulants in critical illness notwithstanding, compelling observations of coagulopathy and high rates of VTE in COVID-19 raise the possibility that heparin may benefit patient outcomes. The utility of heparin as an anticoagulant in COVID-19 was first posited by a retrospective report of 449 patients with COVID-19 from Wuhan, China, where prophylaxis in medical patients is relatively uncommon due to a low incidence of VTE (48). In this cohort, 350 patients received no heparin therapy (neither low-dose prophylactic nor high-dose therapeutic), whereas 99 had received low-dose prophylactic doses of heparin. Patients with an elevated D-dimer (≥6-fold higher than the upper limit of normal) or elevated sepsis-induced coagulopathy scores that received prophylactic heparin had ~20% lower mortality than patients who had not (38). It has also been reported that intravenous tissue plasminogen activator, a potent thrombolytic, can transiently improve oxygenation in COVID-19-related acute respiratory distress syndrome, supporting clinical relevance of thrombosis in severe disease (41).

Since these initial reports, there has been one study published and two studies available in preprint format that have investigated the effects of therapeutic heparin in COVID-19. The largest available study evaluating anticoagulation was a retrospective analysis of 2,773 patients with COVID-19 in the Mount Sinai Health System (29). In patients requiring invasive mechanical ventilation included in this cohort, anticoagulation was associated with an in-hospital mortality of 29.1% compared with 62.7% for patients who did not receive anticoagulation. In contrast, this study found that patients who received anticoagulation were significantly more likely to require invasive mechanical ventilation. This report was retrospective, and the rationale for anticoagulation was not directly investigated, thus making these observations difficult to interpret. In a smaller retrospective cohort study evaluating 44 patients, those who received heparin had improved coagulation parameters and normalized immunity as evidenced by increased lymphocyte counts and decreased interleukin (IL)-6 levels compared with control subjects (35). Another group observed that initiation of heparin for 27 patients infected with COVID-19 improved oxygenation; this study did not include a control group (26). Based on these limited data, clinical treatment guidelines for COVID-19 have not yet recommended the use of therapeutic heparin or other forms of therapeutic anticoagulation (25). To address this question, a total of 18 clinical trials, 9 of which are recruiting, have been registered with the National Institutes of Health (https://www.clinicaltrials.gov/; as of June 2, 2020) to investigate the utility of therapeutic anticoagulation in COVID-19.

PRECLINICAL EVIDENCE FOR HEPARIN AS A SARS-CoV-2 ANTIVIRAL

Beyond anticoagulation, there may be alternative beneficial mechanisms of action for heparin in patients with COVID-19 including direct SARS-CoV-2 antiviral activity. In a similar fashion to the related viruses severe acute respiratory coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), host cell fusion and entry are thought to be accomplished in SARS-CoV-2 infection via binding of the viral spike protein to host angiotensin-convert-

ing enzyme 2 (ACE2) receptors. Cofactors for this binding are incompletely understood for SARS-CoV-2; however, in vitro studies have demonstrated that cell surface heparan sulfate (the class of glycosaminoglycans of which heparin is composed) is essential for entry and infectivity with human coronavirus NL63 (23) and SARS-CoV (19). Heparan sulfate is thought to interact with the spike protein as an adhesion molecule receptor, which may be the first step in facilitating the interaction of SARS-CoV and the ACE2 receptor (23). It has recently been discovered that concordant with other coronaviruses, the SARS-CoV-2 spike protein also interacts with heparan sulfate, and with a higher affinity than either SARS-CoV or MERS-CoV spike proteins (17). In this study by Kim et al., the SARS-CoV-2 spike protein demonstrated extremely strong (and nearly irreversible) binding to heparin using surface plasmon resonance.

Our developing understanding of the virology of SARS-CoV-2 suggests the biologic plausibility of heparin as an antiviral. Theoretically, heparin may bind the SARS-CoV-2 spike protein and function as a competitive inhibitor for viral entry, thus decreasing infectivity. Interestingly, shorter-length heparins, comparable to those found in therapeutic low-molecular weight heparin, did not appreciably bind the spike protein (17), suggesting that low-molecular weight formulations may be less likely to have direct antiviral activity through competitive spike protein binding. If clinical trials demonstrate benefit of unfractionated heparin therapy, its effect could be partially due to this theoretical antiviral activity, rather than solely due to its anticoagulant properties (38). As such, clinical trials with heparin should evaluate disease course and time to clearance of infection, as these outcomes would support direct antiviral activity.

Despite the promise of this concept, no clinical data linking heparin therapy to meaningful antiviral outcomes exist. However, the use of heparin and other glycosaminoglycans as antiviral therapy has significant potential for future clinical applications. The utilization of heparan sulfate as a cofactor for viral entry appears to be conserved across the human coronavirus viruses as discussed, as well as the hepatitis C virus and herpesvirus family (8, 37). With a more in-depth understanding, this therapeutic strategy could be optimized for COVID-19, which may inform broad antiviral treatment with heparin and heparin-like drugs for future zoonotic coronaviruses and other viral pathogens.

ANTI-INFLAMMATORY EFFECTS OF HEPARIN-LIKE DRUGS: RELEVANCE TO COVID-19

Heparin is known to have anti-inflammatory effects both in the vasculature and in the airway, which could beneficially impact COVID-19-associated inflammation. Heparin binds to and modulates the activity of many proteins that mediate inflammation including IL-8, platelet growth factor 4 (PGF4), stromal-derived factor 1a, neutrophil elastase, P- and L-selectin, CD11b/CD18, major basic protein (MBP), and eosinophil cationic protein (ECP; 13, 47). The anti-inflammatory effects of heparin and its constituent heparan sulfate glycosaminoglycan fragments fall into two general mechanisms: 1) dampening of inflammation through interaction with proinflammatory proteins and 2) preventing adhesion and an influx of inflammatory cells to a diseased area.
There are innumerable studies that have demonstrated that heparin can dampen inflammation through its interaction with key inflammatory mediators. The proinflammatory transcription factor nuclear factor-κB (NF-κB), which has been found to be involved in the pathogenesis of SARS-CoV, the virus underlying the 2003 severe acute respiratory syndrome (SARS) epidemic (16), leads to the production of downstream inflammatory cytokines and other immune response proteins including tumor necrosis factor-α (TNF-α), IL-1β, IL-6, and IL-8 (13, 47). Heparin has been observed to directly dampen NF-κB signaling in LPS-stimulated human endothelial cells and human monocytes (21). Similarly, a synthetic heparin-like drug has recently been developed that neutralizes high mobility group box 1 (HMGB1; 5), a proinflammatory mediator that is known to play a role in the pathogenesis of viral infections (15). With respect to inflammatory cell infiltration, a phenomenon that has been observed pathologically in COVID-19 (2, 39), heparin can directly interact with vascular endothelial cells leading to reduced recruitment of the innate immune system and direct inhibition of neutrophil activation (13). More broadly, heparin has been shown to dampen inflammation in other preclinical models characterized by robust inflammation including pancreatitis (12) and sepsis (33).

Clinically, the use of heparin as an anti-inflammatory agent has shown limited evidence of benefit in human diseases including inflammatory bowel disease, asthma, reactive airways disease, and acute coronary syndrome (13, 24). Despite this clinical evidence, heparin has not been approved by the US Federal Drug Administration as a direct anti-inflammatory for any medical condition.

**POTENTIAL ADVERSE AND OFF-TARGET EFFECTS OF HEPARIN THERAPY**

The use of heparin as a therapeutic anticoagulant is associated with a 10–15% risk of significant bleeding (11, 27).
Factors that may increase bleeding risk are older age, worse illness severity, recent trauma or surgery, cardiopulmonary resuscitation, longer hospital stay, and decreased white blood cell and platelet counts (11, 27). Many of these risk factors for bleeding are commonly seen in patients with COVID-19. A second, albeit rare, complication of heparin therapy is HIT, which is estimated to occur in 0.2–3% of patients who receive heparin (4). This feared adverse effect is driven by the development of antibodies specific to the protein platelet factor 4, which leads to life-threatening thrombocytopenia and paradoxical development of thrombosis.

It is also possible that the intended effect of heparin (i.e., anticoagulation) can interrupt lung-protective processes of coagulation that may improve host survival in COVID-19. Although critical illness-associated intravascular thrombosis has been recognized as harmful in animal models of lung injury (44), coagulation occurring within alveoli and airways has generally been found to be lung protective (9, 34). This is particularly notable in animal models of viral pneumonia, in which transgenic loss of epithelial tissue factor markedly worsened animal mortality after influenza infection (3). Transgenic loss of endothelial tissue factor, conversely, had no effect on influenza-induced injury. It is therefore possible that intra-alveolar coagulation may serve a teleological function of isolating pulmonary pathogens, protecting the host from disseminated infection. Such divergent effects of intra-alveolar and intravascular coagulation may in part explain the muted benefits of anticoagulants [including inhaled heparin (6)] in randomized controlled studies of pneumonia.

Finally, heparin may have many other unrecognized effects—both protective and harmful—arising from its heterogeneous structure. As noted, unfractionated heparin is composed of a mixture of distinct biologically derived (i.e., porcine intestinal mucosae) heparan sulfate polysaccharides, which on balance not only is enriched in a pentasaccharide sequence necessary for AT3 activation (and thus anticoagulation) but also displays a wide variety of other sulfation sequences. These non-anticoagulant sulfation sequences allow heparin binding to various growth factors, potentially exerting both organ-protective (46, 49) and organ-harmful (14, 20) effects.

CONCLUSIONS

There is a paucity of pharmacologic therapies for COVID-19. Although heparin may prove beneficial in treating the coagulopathy of this disease, utilization of therapeutic anticoagulation before the development of thrombosis in COVID-19 has not been systematically evaluated. Additionally, although heparin is known to possess non-anticoagulant effects that may be beneficial in COVID-19 (i.e., direct antiviral and anti-inflammatory), the balance between its benefits and risks should be considered. Given the potential benefits (and uncertain risks) of therapeutic heparin (see Fig. 3), tempered by the failures of previous studies targeting coagulopathy in critical illness, randomized clinical trials of heparin in COVID-19 are urgently needed.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.A.H., W.B.L., J.F.C., C.J.L.-A., and E.P.S. conceived and designed research; J.A.H., W.B.L., and E.P.S. performed experiments; J.A.H., W.B.L., J.F.C., C.J.L.-A., and E.P.S. drafted manuscript; J.A.H., W.B.L., J.F.C., and C.J.L.-A. edited and revised manuscript; J.A.H., W.B.L., J.F.C., C.J.L.-A., and E.P.S. approved final version of manuscript.

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