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The old but new: Can unfractioned heparin and low molecular weight heparins inhibit proteolytic activation and cellular internalization of SARS-CoV2 by inhibition of host cell proteases?

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ABSTRACT

Currently, our world is facing the 2019 Novel Coronavirus (COVID-19) outbreak and tremendous efforts are made for developing drugs to treat and vaccines to prevent the disease. At present, there is no specific antiviral drug or vaccine for COVID-19. The pathogenic infectivity of the virus requires the S1 subunit of the spike (S) protein to bind the host cell receptor, angiontensin converting enzyme (ACE2). While the binding to host cell receptor is the first step of infection, the entrance of the virus into the cell needs the cleavage of S1–S2 subunits to expose S2 for fusion to cell membrane via host proteases including cathepsins, cell surface transmembrane protease/serine (TMPRSS) proteases, furin, trypsin and factor Xa. Previous in vitro studies have shown that factor Xa inhibition can decrease viral infectivity. We suppose that host cell proteases including furin (as expressed highly in lungs), factor Xa and cathepsin are possible targets to decrease viral burden, therefore unfractioned heparin and low molecular weight heparin-LMWH (specifically dalteparin and tinzaparin for their anti inflammatory action) can be potential inhibitors of multiple endoproteases involved in virus infectivity. Our hypothesis needs to be tested in in vitro and clinical studies, however as we are in an urgent situation as the burden of SARS-CoV2 is increasing all around the world, we recommend the usage of unfractioned heparin or LMWH in intensive care unit (ICU) and non-ICU hospitalized patients with the risk–benefit judgement of the clinician. Whether our hypothesis is clinically applicable and successful in decreasing viral infection will be evaluated for further studies.

Introduction

Currently, our world is facing the 2019 Novel Coronavirus (COVID-19) outbreak and tremendous efforts are made for developing drugs to treat and vaccines to prevent the disease [1]. At present (up to 28 March when this paper was written) there is no specific antiviral drug or vaccine for COVID-19 [2]. Although most patients develop a mild disease, patients including those with higher ages and patients with comorbidities like hypertension, diabetes mellitus and chronic obstructive pulmonary disease [1]. Although the pathogenic pathways of SARS-CoV2 are not fully understood, as we know that SARS-CoV2 shares 89% similarity with SARS-CoV, we hypothesized that we can offer a treament option originating from SARS-CoV pathogenesis.

Medical hypothesis

SARS-CoV2 is a single stranded RNA virus that is characterized with Spike (S) proteins projecting from the virion surface. The S protein contains two subunits (S1 and S2). The S1 subunit has a receptor binding domain (RBD) that interacts with host cell receptor that is angiontensin converting enzyme (ACE2). After binding the S2 subunit forms fusion between the virus and host cell membranes [3]. However, our experiences from SARS-CoV have shown that the proteolytic action of host proteases are very important for the viral entry to the host cell. While the binding to host cell receptor is the first step of infection, the entrance of the virus into the cell needs the cleavage of S1–S2 subunits to expose S2 for fusion to cell membrane [4]. The cellular proteases including cathepsins, cell surface transmembrane protease/serine (TMPRSS) proteases, furin, trypsin that have been shown to proteolitically process the spike protein [4]. One of these proteases is Factor Xa that has been shown to facilitate to activate SARS-CoV entry into the host cells [5]. In the study by Du L et al, after the SARS-CoV outbreak, 13 inhibitors of proteases which might potentially correspond to cleavege of S protein and be a candidate to supress infection were screened.

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The results showed that Factor Xa can effectively cleave S1/S2 subunits of SARS-CoV which can be inhibited by BEN-Hcl, an inhibitor of series of proteases including serine proteases such as thrombin and Factor Xa. The levels of cleavege of Factor Xa in infected target cells were correlated with viral infectivity and the cleavage was effectively blocked by BEN-Hcl [5]. Previously small molecules targetting proteases (papain like protease 2- helicase-cathepsin L inhibitors) have been studied as potential therapeutic agents against SARS-CoV [6,7]. Among these proteases furin as highly expressed in lungs, can be thought to be involved in the cleavage process of SARS-CoV2 [8]. A recent article points out that the spike glycoprotein of SARS-CoV2 is containing a furin-like cleavege site absent in other CoVs, so that furin inhibitors can be tested as new targets [9].

Evaluation of the hypothesis

When we combine this knowledge with mechanism of actions of unfractioned heparin and low molecular weight heparins, that are inhibitors of several proteases like factor Xa, thrombin, furin and cathepsin-L, we hypothesize unfractioned heparin and low molecular weight heparins (LMWH) can be candidates for targetting protease cleavage and cellular entrance of SARS-CoV2 [10]. A study that investigates antifibrotic effects of heparin has shown that heparin interfered with furin-like proprotein activation of platelet latent transforming growth factor β1 [11]. Apart from its use as anticoagulant, unfractioned heparin and LMWHs have shown to have poteantial applications for other purposes such as allergic diseases and malignancies [12]. As we know, hyperinflammation and macrophage activating syndrome (MAS) is complicating COVID infection leading to capillary leakage and Acute Respiratory Distress Syndrome (ARDS) [13,14]. According to that, because of their anti inflammatory and antiproliferative functions; usage of unfractioned heparin, tinzaparin and dalteparin can be beneficial [15,16]. According to the knowledge we have on how SARS-CoV and SARS-CoV2 infect the host cells via proteases, unfractioned heparin and LMWH can be potential inhibitors of multiple endoproteases (including tissue proteases and matrix metalloproteinases in cell signalling and inflammation) involved in virus infectivity [17]. Our hypothesis needs to be tested in in vitro and clinical studies, yet we could not be able to have clinical experince as pediatric patients have slight symptoms mostly and rarely need intensive care unit (ICU). However as we are in an urgent situation as the burden of SARS-CoV2 is increasing all around the world, we remommend the following clinical usage of heparin.

- The prophylactic use of minidose heparin or prophylactic doses of LMWH (especially dalteparin or tinzaparin) can be used for hospitalized non-ICU 2019-nCoV patients with a normal coagulation profile and normal platelet counts in order to decrease viral load of host cells and prevent the involvement of lower respiratory tract.
- Use of minidose or conventional doses of unfractioned heparin or prophylactic or treatment doses of LMWH (especially dalteparin or tinzaparin) can be used with the consideration of patient's bleeding or thrombotic tendency in case of disseminated intravascular coagulation (DIC) in order to decrease inflammation and viral load in lower respiratory tract and control DIC. The risk-benefit ratio when using in ICU patients with coagulopathy should be judged by the clinician.

Conclusion

Whether our hypothesis is clinically applicable and successful in decreasing viral infection will be evaluated for further studies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109743.

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