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Nebulised Unfractionated Heparin as an Adjunct Treatment for COVID-19 Pneumonia: Potential to Avoid Bleeding Complications with Possibly Similar Degree of Benefits – Strong Scientific Rationale

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Abstract

Nebulised unfractionated heparin (UFH) has a strong scientific and biological rationale and warrants urgent investigation of its therapeutic potential, for COVID-19-induced acute respiratory distress syndrome (ARDS).

COVID19 induced ARDS displays the typical features of diffuse alveolar damage with extensive pulmonary coagulation activation resulting in fibrin deposition in the microvasculature and formation of hyaline membranes in the air sacs.

Abstract

Patients infected with SARS-CoV-2 who manifest severe disease have high levels of inflammatory cytokines in plasma and bronchoalveolar lavage fluid and significant coagulopathy. There is a strong association between the extent of the coagulopathy and poor clinical outcomes. The anti-coagulant actions of nebulised UFH limit fibrin deposition and microvascular thrombosis. Trials in patients with acute lung injury and related conditions found inhaled UFH reduced pulmonary dead space, coagulation activation, microvascular thrombosis, and clinical deterioration, resulting in increased time free of ventilatory support. In addition, UFH has anti-inflammatory, mucolytic and anti-viral properties and, specifically, has been shown to inactivate the SARS-CoV-2 virus and prevent its entry into mammalian cells, thereby inhibiting pulmonary infection by SARS-CoV-2. Furthermore, clinical studies have shown that inhaled UFH safely improves outcomes in other inflammatory respiratory diseases and also acts as an effective mucolytic in sputum-producing respiratory patients. UFH is widely available and inexpensive, which may make this treatment also accessible for low- and middle-income countries. These potentially important therapeutic properties of nebulised UFH underline the need for expedited large-scale clinical trials to test its potential to reduce mortality in COVID-19 patients but more research warranted.

Keywords: *COVID-19, ARDS, SARS, Nebulised heparin, Unfractionated heparin, SARS-CoV-2.*

Introduction:

COVID19 ARDS patients typically have higher plasma markers of coagulation markers and abnormalities such as high D-dimers, increased prothrombin time and a lower platelet count leading to widespread Endothelial dysfunction and microvascular and macrovascular pulmonary arterial thrombosis leading to high dead space and impaired oxygenation in the absence of significant decrease in pulmonary compliance which are the specific pulmonary findings in severe COVID-19. Post-mortem studies and lung biopsies of COVID19 patients with ARDS demonstrated pulmonary fibrin deposition with hyaline membranes in the alveolar spaces and extensive pulmonary microvascular thrombi in the arteries, small arteries, and arterioles **[**1-9**]**

Another explanation for severe hypoxaemia is the loss of lung perfusion regulation and hypoxic vasoconstriction and deposition of microthrombi in small pulmonary vessels, arteries and capillaries with consequent refractory hypoxemia.

Pathophysiology:

The pathophysiology of COVID-19 pneumonia and ARDS is characterised by diffuse alveolar damage, hyperinflammation, coagulopathy, DNA neutrophil extracellular traps (NETS), hyaline membranes and microvascular thrombosis.

Role of SC or IV heparin therapy has been well documented in many larger RCTs and has shown significant mortality benefit but with its attendant bleeding risk in certain patients approximately in 5 to 10 % of patients receiving systemic heparin.

Microvascular thrombosis is the main culprit:

Fibrin accumulation in pulmonary capillaries and venules, which leads to microvascular thrombosis, is an early feature of ARDS and the extent of this fibrin accumulation correlates with the severity of lung injury **[**10-13**]**

In response to inflammatory cytokines, the pulmonary capillary beds, venules and arterioles express tissue factor on endothelial cells and this triggers the conversion of plasma coagulation factors to fibrin **[**14**]**. Cytokine activation of NETosis and the presence of intravascular NETs are further associated with the initiation of thrombosis in arteries and veins, and NETs circulating at high levels in COVID-19 can trigger micro embolic occlusion of small blood vessels in the lungs, heart and kidneys **[**24, 25**]**. Extensive microvascular thrombosis has been demonstrated in histological studies of ARDS Angiographic studies showed the extent of microvascular obstruction correlated with the severity of respiratory failure and with mortality. Microvascular thrombosis increases lung dead space and the increase in dead space or its bedside surrogate ventilatory ratio was shown to be an independent marker of mortality in ARDS **[**15,16**]**. Microvascular thrombosis also causes increased pulmonary vascular resistance, which may result in right heart failure **[**17**]**.

There is a strong association between the extent of the coagulopathy and poor clinical outcomes. In a case series of 183 COVID-19 patients, those who died had markedly elevated D-dimers, elevated fibrin degradation products, longer prothrombin time and activated partial thromboplastin time compared to survivors on admission, often meeting criteria for disseminated intravascular coagulation **[**18**]**. Similar coagulation abnormalities were described in other case series and elevated D-dimer levels were associated with clinical outcomes **[**19,20**]**. In a Dutch case series of 184 COVID-19 positive patients, all

of which received van Haren et al. Critical Care (2020) 24:454 Page 3 of 11 pharmacological thromboprophylaxis, the cumulative incidence of a composite outcome comprised of symptomatic pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism was 49%. The majority of thromboembolic events were PE (87%) **[**21**]**.

Another recent case series showed that COVID-19 ARDS patients developed significantly more thrombotic complications mainly Pulmonary embolism.

Clinically Proven beneficial effects of nebulised Un-fractionated heparin (UFH):

Anti-coagulant effects:

Nebulised UFH targets pulmonary fibrin deposition and inflammation, and local administration to the lungs allows higher dosages and increases local efficacy, reduces the risk of systemic bleeding and is more effective than intravenous administration **[**22,23 **]**. Importantly, previous studies have shown that following nebulisation, UFH does not enter the systemic circulation significantly which means it can be used in addition to systemic therapeutic or prophylactic anti-coagulation without concerns of furthering systemic anti-coagulation. The use of nebulised UFH in other respiratory settings was not associated with local side effects in the lung including bleeding **[**23-27 **]**.

One study on healthy volunteers to see the effect of inhaled heparin on lung function and coagulation by inhaling 32,000 IU, as a lower respiratory tract dose, of UFH, they concluded that it did not affect pulmonary function. A dose-dependent anticoagulant effect could be demonstrated on the circulating blood (anti factor Xa, activated partial thromboplastin time) and the endothelial cells as release of tissue factor pathway inhibitor. {28**]**

Many other studies have shown the anticoagulant action of inhaled UFH in dose dependent manner

Anti-inflammatory effects

Inhibition of inflammatory cytokines involved in COVID-19 pathophysiology and the inhibition of inflammatory cell recruitment into tissues via blocking many of the key adhesion molecules expressed on vascular endothelium, improvement in lung function and increased nitric oxide release **[** 29-32 **]**. Nebulised heparin decreases pro-inflammatory cytokines in lung tissue and the expression of NF-kB and TGF-β effectors in alveolar macrophages **[**33,34 **]**

Anti-viral effects:

Several studies found heparin competes with heparan sulphate for bacterial and viral adhesion and may therefore limit pathogen invasion **[**35,36**]** For example, heparin limits adhesion of P, aeruginosa, Burkholderia cenocepacia and pseudomallei, Legionella pneumophila, S aureus, Strept. pyogenes and pneumoniae, RSV and influenza A **[**37, 38**]**. Human and animal studies suggest these actions may reduce the development of pneumonia and bacteraemia **[**39**]**. Previous studies demonstrated that UFH prevented SARS-associated coronavirus and other enveloped viruses such as HIV and HSV from attaching to and invading mammalian cells **[**40-46**]**. A recent study demonstrated that the SARS-CoV-2 Spike S1 protein receptor-binding domain attaches to UFH and undergoes conformational change that may prevent it from binding to ACE-2 **[**47**]** and hence less chances of replication and infecting human cells. Importantly, the binding of heparin to the receptor binding domain of the SARS-CoV-2 Spike S1 protein is orders of magnitude stronger for full-chain length heparin than low-+molecular weight heparins (LMWHs) **[**48**]**.

Two Multicentre trial to Assess the Efficacy and Safety of UFH for the Treatment of COVID 19 with the goal to investigate the effects of nebulised UFH on patients who may require ICU care with standard care and another multinational multi-centre randomised open-label trial to determine the difference of outcome between standard care and nebulised UFH, compared to standard care alone in terms of reduce Mechanical ventilation day and LOS are also under way and these trial will shed light on the potential role of UFH on COVID 19 management

Discussion and Rational

For more than 2 decades, Nebulized medicines (including bronchodilators, antibiotics, mucolytics and many other medicines) have been used in primary pulmonary disorders viz. asthma, COPD, severe bronchopulmonary infections, colonized tracheobronchial tree as prophylaxis or treatment of infection in cystic fibrosis patients etc. **[**49**]** UFH has been utilised in the treatment of CF patients for its mucolytic properties with no safety issues and in particular inhaled nebulised UFH has been used safely in patients who are also receiving system anti-coagulation **[**50**]**.

In Acute lung injury and many more respiratory diseases inhaled therapies has time tested established role considering the large surface area of lung with highly vascular parenchyma and hence large absorption capacity with resultant effects in COPD, asthma and other bronchopulmonary diseases with the main aim to provide the appropriate dosages of appropriate medicine at the best site of action (i.e at the main pathophysiological site of the disease) and to minimize the side effects of the medicine and to get best benefits of medicines.

Considering the significant numbers of bleeding complication especially in vulnerable / high risk COVID patients, nebulized heparin could be considered as an adjunct / alternative to the treatment especially in mild / moderate severe COVID 19 cases or where high doses of heparin are needed but at the same time high risk of bleeding coexists in patient due to other comorbidities .

The potential of airways and alveoli to absorb particles and chemical substances is impressive. The layer of liquid and surfactant covering the epithelial cells is continuous and offers relatively uniform diffusion possibilities. Inhaled particles can be observed submersed in the aqueous lining layer and adjacent to epithelial cells **[**51**]**. This allows interaction with these cells as well as diffusion through them into interstitial space and vascular and alveolar structures.

Dixon et al **[**52**]** have examined the effects of nebulised heparin in a pilot study involving 16 COVID patients, with 4 different doses protocol to assess effect of inhaled heparin on respiratory function and systemic coagulation factors, as well as its products in bronchoalveolar lavage fluid (BAL). they concluded that inhaled heparin did not cause significant changes in the ratio of arterial oxygen partial pressure (PaO2) to inspired oxygen fraction (FiO2), dead space or compliance. However, a trend for an increasing systemic anticoagulant effect with higher doses was observed.

COVID 19 primarily behave as acute lung injury with typical pulmonary parenchymal changes, marked inflammation, interstitial edema, micro and macro vascular thrombosis, alveolar fibrin deposition, hyaline membrane formation and fluid accumulation **[**53**]**. It has been shown, on one hand, that pulmonary inflammation can cause local disturbances in fibrin turnover; and on the other hand, it is known that an intra-alveolar pro-coagulant state with increased fibrin deposition and limited breakdown may enhance inflammatory changes **[**54-56**]**. As suggested by a number of experimental and clinical studies, heparin has anticoagulant and fibrinolytic properties as well as anti-inflammatory effects. Given by nebulisation, this substance had positive effects in animal models of ALI or lung fibrosis **[**57,58**]**.

The translation of a potentially beneficial effect of inhaled heparin in experimental models of ALI to clinical practice has not yet been achieved; and many important questions need to be addressed by scientific evidence including time to start nebulized heparin, dose,(loading dose and maintenance dose and duration of inhaled heparin and its adjustment with the severity of disease and need for systemic heparin based on the dimer level and evidence of other systemic coagulation and the risk of bleeding assessment in each individual patients based on the risk benefits and to regularly monitor the effects of inhaled heparin on the clinico-radiological improvement in COVID with the resolution of the ground glass opacities and hyaline membrane resolution and improvement in hypoxia. To answer above concerns well designed large scale randomized controlled multicentre trials are needed with well-defined design and protocol in place to determine the efficacy of inhaled heparin in COVID pneumonia

Conclusion

Role of LMWH heparin or UF heparin has not been well documents in the literature for treatment of COIVD 19.

This article tries to elaborate the concept of possible role of nebulized unfractionated heparin considering the hypercoagulable, prothrombotic embolic pathophysiology of COVID19 with primary pulmonary predilection. Nebulized UFH will lead to local deposit of heparin (which is a locally acting molecule) at high concentration in the highly permeable and highly vascular pulmonary parenchymal bed and hence significantly large amount of UFH can be absorbed rapidly from the large surface area of lung in efficient way and with consequent faster recovery and morbidity and mortality benefits and less drug dose delivery by the SC route with the simultaneous avoidance of the bleeding complications especially in adult patients and those patients who are at risk of bleeding due to their inherent bleeding diathesis or other risk factors like cavitary tuberculosis, Aspergilloma, previous/ recent history of Brain haemorrhage/ brain surgery/ brain tumour or Gastrointestinal bleed and many more high risk patients. The main drawback of this approach is this can be considered for only those patient which have primary pulmonary clinical or radiological involvement and not suitable for multisystem thromboembolic phenomenon where addition systemic doses would be definitely required. However large case controlled trial would be needed to establish the role of inhaled UFH in the management of COVID 19 mild / moderate/ severe case and COVID19 ARDS and the safety profile of the inhaled UFH . Many studies are underway and soon we would be having better insight about the efficacy of nebulized UFH for COVID pneumonia as an adjunct or alternative therapy to systemic heparin.

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