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INHALED NEBULISED HEPARIN A NEW WAY TO IMPROVE LUNG FUNCTION: A REVIEW

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ABSTRACT

Bronchoconstriction and airway inflammation are the main conditions of COPD and other lung diseases. Acute exacerbation of these conditions often lead to dyspnea, cough and increased sputum production, which ultimately cause significantly reduced health related quality of life, and increased morbidity and mortality. Inhaled corticosteroids, bronchodilators and beta $_2$agonists are being used in the treatment of COPD and asthma. However, it is reported that there is an increased risk of pneumonia in patients with COPD receiving regular inhaled corticosteroids and therefore we need to find other safer treatments. Heparin is clinically being used as an anticoagulant, but it has non anticoagulant properties too. It is shown in clinical experiments that non anticoagulant properties of heparin can be used to inhibit inflammatory responses. A study by Farzin Ghiazi reported that the effectiveness of nebulized heparin is comparable with a potent inhaled corticosteroids among ventilated patients. Heparin and its related derivatives have also shown to benefit patients with asthma. Studies have revealed that Heparin inhalation reduced bronchial hyper reactivity and prevents exercise-induced asthma. Potential mechanisms in anti-inflammatory effects of heparin have been discussed in a review by Young. Considering the results of studies, we can conclude that heparin could have potential anti inflammatory effects in treating lung disease. The purpose of this review is to consider all the relevant available study reports to point out that inhaled nebulised heparin can be considered for improving lung function in chronic pulmonary diseases.

KEYWORDS: Inhaled nebulised heparin, Inflammation, Corticosteroids, COPD, Lung disease.

INTRODUCTION

Bronchoconstriction and airway inflammation are the main conditions of COPD and other lung diseases also characterised by progressive airflow limitation and air trapping, leading to lung hyperinflation and exercise limitation. Acute exacerbation of these conditions often lead to dyspnoea, cough and increased sputum production, which ultimately cause significantly reduced health related quality of life, and increased morbidity and mortality.

Mechanical ventilation is an important tool in the management of respiratory failure in the critically ill patient. It is required for the management of respiratory failure resulting from various clinical conditions such as acute respiratory distress syndrome (ARDS), pneumonia, sepsis, chronic obstructive pulmonary disease, and asthma. Although mechanical ventilation can be a lifesaving intervention, it is known to carry several side effects and risks.[1] Mechanical ventilation can increase the level of inflammatory mediators within the lungs, and treatment with the antagonists of these mediators may reduce it.[2] A number of potential targets have been identified in preclinical studies. Increased levels of several inflammatory mediators [including tumor necrosis factor (TNF)α, interleukin-6, and interleukin-10 were found in subjects injurious mechanical ventilation.[3] TNF has been consistently implicated in the pathogenesis of acute lung injury (ALI)/ventilator induced lung injury, both clinically and in experimental models.[4]

In addition, lower TNF-α levels in both the serum and bronchoalveolar lavage fluid from patients at risk for ARDS exhibited a good negative predictive value for ARDS development.[5] Heparin and related molecules can bind electrostatically to the positively charged nuclear localization sequence of NF-κβ and prevent it from translocation to the nucleus. Blocking of this transcriptional factor can potentially reduce inflammatory gene activation and regulate the gene expression and production of proinflammatory cytokines, chemokines, and adhesion molecules.[6]

Unfractionated heparin inhibits lipopolysaccharide induced activation of endothelial cells through inhibition of p38MAPK and NF-κβ. Heparin has been shown to bind to the surface of neutrophils and can inhibit their degranulation. Further, heparin is able to inhibit

neutrophil activation in response to thrombin-stimulated platelet products, in addition to inhibiting thrombin-induced platelets.[7]

Currently, there is no cure and treatments do not prevent the steady worsening of symptoms such as struggling to breathe, poor quality of life and often, early death. Inhaled corticosteroids, bronchodilators and beta $_2$agonists are being used in the treatment of COPD and asthma. However, it is reported that there is an increased risk of pneumonia in patients with COPD receiving regular inhaled corticosteroids and therefore we need to find other safer treatments.[8] Heparin is clinically being used as an anticoagulant, but it has non anticoagulant properties too. It is shown in clinical experiments that non anticoagulant properties of heparin can be used to inhibit inflammatory responses. The objective of this review is to consider and summarize the literature supporting anti-inflammatory role of heparin to provide evidence about the clinical effectiveness and safety of heparin in inflammatory conditions.

DISCUSSION

Heparin is known for its anticoagulant properties and so it is being used currently in treatment and prevention of thrombotic events like deep vein thrombosis, pulmonary emboli, acute coronary syndromes, and ischemic cerebrovascular events, prevention of thrombosis and hemodialysis.[9,10] Apart from its anticoagulant effects, there are several studies which have shown that heparin possesses various anti-inflammatory and immune modulatory properties and the mechanisms of anti-inflammatory actions of heparin have been discussed recently.[11,12] A study by Lever R, et al showed anti-inflammatory effects in an in vivo model of peritoneal inflammation using locally administered heparin at the site of inflammation.[13] Areview article by Michell NP et al stated that a result of their intense negative charge, the glycosaminoglycans that constitute heparin have diverse biological effects including potent anti-inflammatory actions.[14]

A study by Stelmach et al.of provoke challenge tests with histamine or leukotriene D4 before and after inhalation of heparin; showed that heparin (5000Iu) decreases histamine and leukotriene-induced bronchial hyper reactivity compared to placebo significantly.[15] Janis Shute, evaluated the use of inhaled nebulized unfractionated heparin as a treatment for moderate-to-severe COPD and significantly improved lung function and a patient's ability to exercise, without side-effects and additionally, it reduced the labored breathing. It was the first time heparin's effect on lung function has been tested in patients with COPD.[8] Tyrrell DJ, et al have described anti-inflammatory functions of heparin distinct from its anticoagulant

mechanism and presented some in vivo data showing heparin's beneficial effects in various preclinical models of inflammatory disease.[16]

A study by Jensen et al. demonstrated that inhalation of¡32,000 IU of unfractionated heparin as an LRT dose is safe, with respect to pulmonary function and systemic coagulation.[21] This study demonstrates that inhaled heparin has an effect on the circulating blood, by increasing anti-Xa and activated partial thromboplastin time APTT, and on the release of tissue factor pathway inhibitor TFPI from the endothelial cells, whereas no adverse or anti-inflammatory effects were found (platelets, CRP). The present study confirmed this finding by measuring the anti-Xa activity. The small increase in anti-Xa activity probably reflected the fact that most of the heparin that has reached the blood is associated with the endothelial cells.

The concentration of platelets was unaffected by increasing doses of heparin. Platelets were measured in order to document the absence of heparin-induced thrombocytopenia. CRP was largely unaffected by heparin inhalation. A significant decrease over time after inhalation of 100,000 IU heparin must be explained by chance. CRP would not be expected to be affected in normal healthy volunteers without evidence of inflammatory diseases. The large intersubject variation in response to TFPI and anti-Xa demonstrated that knowledge concerning the fate of inhaled heparin in the body is insufficient. As previously mentioned, heparin is stored in endothelial cells, but mast cells and macrophages also serve as reservoirs of heparin.[16] As heparin is also synthesized and metabolized, the pharmacodynamics are likely to be complex. These factors preclude this route of administration for effects other than local, as an anti-inflammatory agent in airway disease.

Probable Mechanism

Although the anticoagulant actions of heparin are well understood, those mechanism underlying its anti-inflammatory effects are not widely known. Potential mechanisms of anti-inflammatory effects of heparin have been discussed completely in a review by Young[12] A study by Janes Shute showed that heparin has unique mucus thinning properties, making it easier for patients to clear their airways.[8] In this study, Heparin made a clinically significant improvement (more than 10 per cent) in lung function measured by the amount of air forcibly exhaled from the lungs in one second after taking the deepest breath possible. Wan JG, et al. chemically modified heparin and this discrete set of the heparin derivatives were tested and shown their anticoagulant and anti-inflammatory activities, such as leukocyte adhesion and transmigration in vitro.[18] In a review article by Ludwig RJ, et al. Heparin and related

polysaccharides have been shown to interfere with leukocyte homing through a variety of effects distinct from their anticoagulant properties.[19] That Heparin can bind to P-selectin, and its anti-inflammatory property is mainly due to inhibition of P-selectin supported by in vitro cell adhesion experiments with heparin.[20]

Safety and Tolerability

Inhaled heparin has also been shown to be safe and without side-effects in patients with cystic fibrosis. Philipp Markart et al studied acute effects of heparin inhalation on lung function and exercise capacity and the safety and tolerability of heparin inhalation Idiopathic Pulmonary Fibrosis patients in an open-label exploratory pilot study.[21] Most studies did not report any unwanted event with heparins when they used them as anti-inflammatory agents whether through systemic or through local (as inhaler or irrigation) administration. The investigators say more research is now needed to confirm the long-term safety of inhaled heparin in patients with COPD and cystic fibrosis.

Pulmonary function was recorded several times after heparin inhalation with all doses of heparin in the present study, but no effect on any of the pulmonary function variables was found. Thus, inhalation of heparin is safe with respect to pulmonary function in healthy volunteers.[22] Similarly, a previous study demonstrated no immediate effects on pulmonary function of a single dose of inhaled heparin.[23]

FIGURES

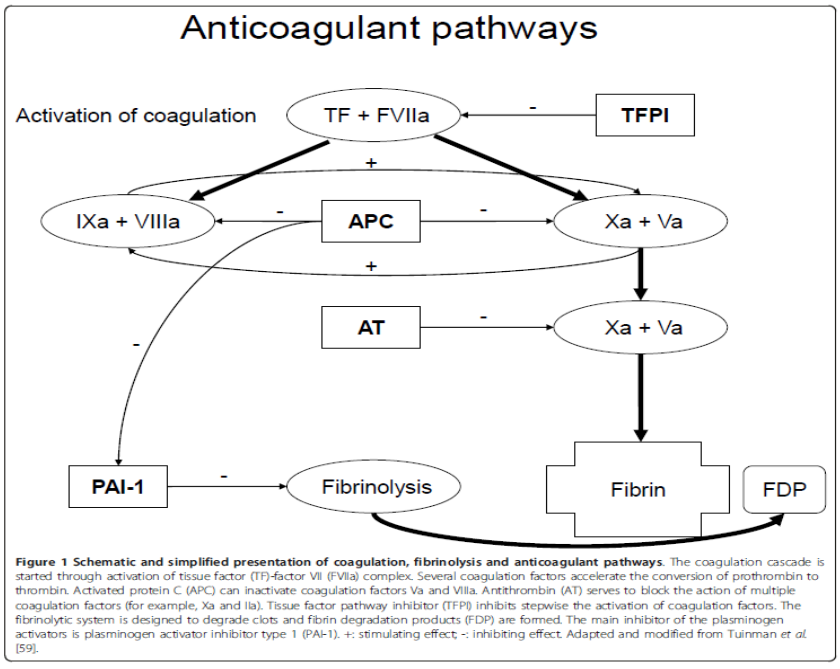

Figure 1 Schematic and simplified presentation of coagulation, fibrinolysis and anticoagulant pathways. The coagulation cascade is started through activation of tissue factor (TF)-factor VII (FVIIa) complex. Several coagulation factors accelerate the conversion of prothrombin to thrombin. Activated protein C (APC) can inactivate coagulation factors Va and VIIIa. Antithrombin (AT) serves to block the action of multiple coagulation factors (for example, Xa and IIa). Tissue factor pathway inhibitor (TFPI) inhibits stepwise the activation of coagulation factors. The fibrinolytic system is designed to degrade clots and fibrin degradation products (FDP) are formed. The main inhibitor of the plasminogen activators is plasminogen activator inhibitor type 1 (PAI-1). +: stimulating effect; -: inhibiting effect. Adapted and modified from Tuinman *et al.* [59].

CONCLUSION

Various studies showed evidence of anti-inflammatory effects of heparin and the probable mechanisms have been over viewed in this article. There are limited number of studies to support the use of inhaled nebulised heparin to improve lung function. so further large clinical trials to be conducted on this aspect inorder to prove the safety and efficacy of this .

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