Efficacy of Nebulized Unfractionated Heparin in Treatment of COPD Patients

Thesis

Submitted For Partial Fulfillment of Master Degree in Pulmonary Medicine

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2017

Acknowledgement

First of all, thanks to **Allah,** *the kind and merciful.*

I would like to offer my sincerest gratitude and immense appreciation to my supervisor **Prof. Emad EL-Din Abd-Elwahab Korraa** *Professor of Chest Diseases, Faculty of Medicine; Ain Shams University, for his faithful guidance and helpful instructions.*

My deepest gratitude and thankfulness are due to **Dr. Hossam Eldin Mohamed Abdel-hamid** *Lecturer of chest diseases of Chest Diseases, Ain shams University, for his generous advice and perpetual supervision.*

I would like to extend my thanks to all the staff and colleagues of Chest Department, Faculty of Medicine, Ain shams University for their true and honest support throughout the whole work.

Particular thanks and special appreciation are due to my Supportive family, without their help this work would not come to light.

Eman Abd El. Hamid

بسم الله الرحمن الرحيم

﴿وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللهِ عَلَيْكَ عَظِيمًا﴾

صدق الله العظيم

سورة النساء آية (١١٣)

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List of Abbreviations

Abb.	Full term

AMP ..... *Adenosine monophosphate*

ATP ..... *Adenosine triphosphate*

CAT ..... *COPD assessment test*

CFTR ..... *Cystic fibrosis conductance transmembrane regulator*

COPD ..... *Chronic Obstructive Pulmonary Disease*

C-X-C R2 ..... *chemokine receptor type 2*

DNA ..... *Deoxyribonucleic acid*

FEV1 ..... *forced expiratory volume in 1st second*

FVC ..... *Forced Vital Capacity*

GAG ..... *Glycosaminoglycans*

GOLD ..... *Global Initiative for Chronic Obstructive Lung Disease*

HIT ..... *Heparin induced thrombocytopenia*

HIV ..... *Human immune diffienency virus*

ICS ..... *Inhaled corticosteroids*

IL ..... *Interleukins*

LABA ..... *Long acting beta2 agonist*

LAMA ..... *Long acting muscarinic antagonist*

LMWH ..... *Low molecular weight heparin*

MMPs ..... *macrophage-derived matrix metalloproteinases*

MRC ..... *Medical Research Council Scale*

NF-κB ..... *Nuclear factor kappa b*

PGP ..... *Proline-glycine-proline peptide*

PLT ..... *Platelet*

List of Abbreviations cont…

Abb.	Full term

PTT ..... *Partial thrombin time*

S.C ..... *Subcutaneous*

SGRQ ..... *St George respiratory Questionnaire*

UFH ..... *Unfractionated heparin*

VEGF ..... *Vascular endothelial growth factor*

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Abstract

Heparin has anti inflammatory effects as Heparin can inhibit the activation of a range of inflammatory cells, an effect that is due in part to the binding and neutralization of inflammatory mediators and enzymes released during an inflammatory response, that would otherwise go on to activate such cells. Likewise, certain enzymes and cytotoxic mediators released from these cells, involved in propagation of the inflammatory response and subsequent tissue damage and remodeling, have also been shown to be inhibited by heparin.

Heparin has potential use in human inflammatory disease and was first assessed for this purpose in the 1960s, in small, subjectively assessed trials. More recently, in controlled studies, heparin has shown potential in the management of clinical asthma and chronic obstructive pulmonary disease (COPD).

Keywords: **C**hronic obstructive pulmonary disease- long acting beta 2agonist- inhaled corticosteroids- matrix metalloproteinases

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality, morbidity and significant cost to health systems. The projection for 2020 indicates that COPD will be the third leading cause of death worldwide (from sixth in 1990), COPD is a preventable and treatable chronic disease, but is frequently underdiagnosed and under-treated in clinical practice ***(Raherison and Girodet, 2009).***

COPD is a common treatable and preventable chronic disease characterized by persistent and progressive airflow limitation caused by increase airway and lung inflammatory response to noxious particles and gases. The main risk factor for COPD is tobacco smoking; other risk factors include outdoor, occupational and indoor air way pollution. Diagnosis of COPD depends on symptoms, history of exposure, family history of COPD and Spirometry ***(Salvi and Barnes, 2009).***

Symptoms of COPD include:

- Dyspnea; progressive and persistent.
- Chronic cough which may be intermittent and not productive.
- Chronic sputum production.
- Attacks of exacerbation (acute worsening of the symptoms).

(GOLD 2015)

Classification of COPD

Spirometry: post bronchodilator forced expiratory volume in first second (FEV1) to forced vital capacity (FVC) ratio <70%.

1. ***GOLD classification of COPD based on post bronchodilator FEV1:***
   - GOLD I Mild COPD FEV1≥ 80% normal
   - GOLD II Moderate COPD FEV1 50-79% normal
   - GOLD III Severe COPD FEV1 30-49% normal
   - GOLD IV Very Severe COPD FEV1 <30% normal
2. ***Combined assessment of COPD***
   - A: gold I, II CAT <10 exacerbations< 1/year
   - B: gold I, II CAT≥10 exacerbations ≥ 2/year
   - C: gold III, IV CAT<10 exacerbations<1/year
   - D: gold III, IV CAT≥10 exacerbations≥ 2/year

(GOLD 2015)

The glycosaminoglycan heparin is a sulphated polysaccharide located in connective tissue mast cells in most mammalian species including humans. Since the discovery many years ago that heparin possesses potent anticoagulant activity ***(McLean, 1916).***

It has been suggested that the primary physiological role of heparin is unlikely to be that of an anticoagulant. Since numerous studies have reported many anti-inflammatory and immunomodulatory properties of heparin in both experimental and clinical settings ***(Tyrell et al., 1999).***

It has been proposed that heparin serves as an endogenous anti-inflammatory molecule, involved in the control and resolution of inflammatory responses ***(Lancet, 1991).***

The anti-inflammatory properties of heparin and related molecules are currently under investigation in various clinical conditions including inflammatory bowel disease, asthma and allergic rhinitis ***(Lever, 2002).***

Of particular relevance to chronic obstructive pulmonary disease (COPD), heparin has been shown to potently inhibit the activity of neutrophil-derived proteases such as elastase and cathepsin G ***(Redini et al., 1988).***

Additional in vitro and in vivo studies have reported inhibition by heparin of other neutrophil activities including degranulation, the respiratory burst and processes involved in neutrophil trafficking into tissues ***(Ramdin et al., 1998)***.

It also has marked anti-inflammatory and antiallergic actions that are mediated by histamine-binding or by blocking the release of histamine and serotonin from platelets ***(Lever and Hoult, 2000).***

It was reported that intrabronchial instillation of heparin diluted bronchial secretions in patients with pulmonary alveolar proteinosis by fragmenting and emulsifying the alveolar content ***(Ramirez et al., 1963).***

Heparin aerosols enhance airway conductance in patient with COPD, So beneficial effect in COPD patient after inhalation of a heparin aerosol might occur as a result of a dual effect removal of secretions from the airways, and bronchial dilatation secondary to anti-inflammatory response ***(Praparin et al., 1968).***

It was proved that daily usage of subcutaneous low molecular weight heparin for one month with inhaled corticosteroids (ICS) and long acting beta 2agonist (LABA) enhance FEV1 and FVC ***(Brown et al., 2006).***

The St. Georges respiratory questionnaire is designed to measure and to quantify health related health status in patients with chronic airflow limitation. It has been shown to correlate well with established measures of symptoms level, disease activity and disability. First part of the questionnaire evaluates symptomatology and second part has two components. First component evaluate activities which are limited by breathlessness or causing breathlessness, second part evaluates impact which cover range of factors including influence on employment, panic, medications side effects, and expectations of health and disturbance of daily Life ***(Jones et al., 1992).***

The Arabic version of SGRQ is conceptually equivalent to the original, and similarly reliable and valid ***(Metwally, 2004).***

Aim of the Work

To detect the effect of nebulized unfractionated heparin on improving symptoms of chronic obstructive lung disease and detect possiable side effects at outpatient clinics.

Chapter 1

COPD

Definition

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person ***(GOLD, 2017).***

Risk factors:

The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute. Besides exposures, host factors predispose individuals to develop COPD. These include genetic abnormalities, abnormal lung development and accelerated aging ***(Lange et al., 2015).***

Worldwide, the most commonly encountered risk factor for COPD is tobacco smoking. Other types of tobacco, (e.g. pipe, cigar, water pipe) and marijuana are also risk factors for