The effect of administration of lycopene on interleukin 8 levels and hospitalization time of patients with chronic obstructive pulmonary disease exacerbations

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Abstract. Background: Exacerbated chronic obstructive pulmonary disease is an acute condition, characterized by persistent air flow limitations, related to the excessive chronic inflammatory response in the airways and lung parenchyma caused by exposure to harmful gases or particles. Increased airway inflammation during exacerbations leads to increased levels of IL-8 and the risk of hospitalization. Lycopene is a carotenoid which has a positive effect on the respiratory system. The purpose of this study was to determine the effect of administration lycopene to IL-8 levels and hospitalization time of patients with COPD disease exacerbations.

Methods: The experimental test with pretest and posttest design for 30 patients with COPD exacerbations in Dr. Moewardi Surakarta Hospital and Dr. Soehadi Prijonengoro Sragen Hospital was conducted from February to March 2018. Samples were taken by consecutive sampling divided into two groups including the treatment group receiving standard therapy and lycopene 1x10 mg/day during treatment and the control group only receiving standard therapy. IL-8 levels and hospitalization time of patients with COPD disease exacerbations were measured.

Results: There were significant differences between the treatment group compared to the control group for a decrease in IL-8 (p = 0.029) and a decrease in hospitalization time (p = 0.000).

Conclusion: The administration of lycopene 1x10 mg/day significantly reduce IL-8 levels and hospitalization time of patient with COPD exacerbations.

Keywords: lycopene, COPD, acute exacerbation, IL-8 level, hospitalization time

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease that is a global health problem that causes an increase in morbidity and mortality, brings social and economic impacts, but can be prevented and treated which is characterized by limited persistent air flow, related to the chronic inflammatory response in the channel lung breath and parenchyma caused by exposure to harmful gases or particles.1 The World Health Organization (WHO) through the Global Burden of Disease Study said COPD was ranked as the sixth leading cause of mortality in 1990, ranked
Cigarette smoke, air pollution, workplace exposure, and other harmful substances will cause an abnormal response of the airways and lungs, causing chronic inflammation involving multi-cells and inflammatory mediators. Inflammatory cells in COPD consist of T lymphocytes, neutrophils, macrophages, eosinophils, epithelial cells, and dendritic cells. Leukotriene B4 (LTB4), interleukin 8 (IL-8), tumor necrosis factor-alpha (TNF-α), IL-1 beta (β), IL-6, and transforming growth factor β (TGF-β) are inflammatory mediators that play a role in the inflammatory process of COPD. Exacerbations in COPD will result in increased cells and inflammatory mediators. The use of bronchodilators coupled with anti-inflammatory agents, antioxidants, and antiproteases is a standard therapy that is expected to prevent the progression of the disease. New research in the provision of anti-inflammatory drugs outside of standard therapy is being developed in an effort to prevent the progression of COPD. The use of currently available anti-inflammatory is considered not yet effective enough because most cases of COPD are resistant to glucocorticoids due to damage to histone deacetylase 2 (HDAC2) caused by exposure to cigarette smoke and oxidative stress.

Lycopene is a carotenoid group that has fat-soluble properties with red pigment, found mostly in tomatoes, and has a positive effect on the respiratory system that can function as an anti-inflammatory in COPD. Proinflammatory cytokine production is suppressed by inhibiting the activation of the nuclear kappa beta factor (NF-κβ) which is an important transcription factor in the inflammatory process and controls IL-8 production. Activation of NF-κβ through translocation and phosphorylation of NF-κβ / p65 κβ kinase (IKK) α and IKKβ inhibitors which then causes transcription of inflammatory genes. Interleukin-8 is the strongest chemoattractant that triggers neutrophil chemotaxis and plays an important role in the inflammatory process in COPD exacerbations. The aim of the study was to analyze the effect of addition lycopene on IL-8 levels and hospitalization time of patients with COPD exacerbations. The benefits of the study by analyzing IL-8 levels as a marker of inflammation and length of stay as a measure of clinical improvement for patients with COPD exacerbations, it is expected to provide improvement in standard management in patients with COPD exacerbations.

Methods

The research was based on clinical trials with quasi-experimental research designs using a purposive sampling technique using pre-test and post-test approaches in the treatment and control groups. The study population was in patients with acute exacerbation of COPD at Dr. Moewardi Surakarta and Dr. Soehadi Prijonegoro Sragen Hospital from February to March 2018. This study was reviewed by the Health Research Ethics Commission Moewardi Hospital with a registration number 98/II/HREC/2018. The total sample of 30 respondents was divided into 2 groups: the treatment and control groups.

The study inclusion criteria were acute exacerbation COPD patients who were clinically diagnosed and treated, over 40 years of age, and were willing to take part in the study by signing the consent form. Exclusion criteria were acute exacerbation COPD patients in ICU care and mechanical ventilation support, kidney disease patients, lung cancer, sepsis, HIV / AIDS, received other additional antioxidant therapy during the study, and had an allergy to lycopene. Uninterrupted criteria are patients who resign or die, and experience side effects or allergic to lycopene.

The stages of the study included patients with acute exacerbation COPD who met the inclusion criteria; an explanation of the purpose of the study was provided and subjects were willing to be involved in the research by signing the consent form. Initial data of the subjects were obtained from medical history taking, physical examination, and chest X-ray and then measured IL-8 levels through venous blood sampling. Subjects were divided into 2 groups: the treatment group through standard COPD exacerbation therapy and the administration of
1x10 mg of lycopene given together with food during treatment. Control group through standard COPD exacerbation therapy. Bronchodilators, antibiotics, corticosteroids, and other supportive therapies are given according to the management procedure of exacerbation of COPD. Subjects were observed every day until clinical improvement was achieved, which was stable and met discharge criteria and measured IL-8 levels again.

Analysis of normally distributed data was carried out parametric test or t-test while the non-parametric distribution was conducted using nonparametric test, namely Wilcoxon test in paired groups, and Mann Whitney test for unpaired groups. The significance level of \( p > 0.05 \) is not significant, \( p <0.05 \) is significant.9

**Results**

Distribution of basic characteristics respondent based on table 1 that \( p \)-value \( \geq 0.05 \), there is no significant difference in all respondents of basic characteristics between the treatment and control groups. Characteristics of respondents by sex; showed no gender differences in the treatment and control groups. All COPD respondents were male.

Characteristics of respondents based on age; showed the results of t-test \( (p = 0.931) \) so that there were no significant differences in the treatment and control groups. Characteristics of respondents based on the level of education of respondents assessed using the Mann Whitney test with a value of \( p = 0.604 \) which means that the level of education between the two groups is not significantly different.

Characteristics of respondents based on work using the Chi-Square Test with results \( p = 0.666 \) and means that the work in the two groups did not difference significantly different.

Characteristics of respondents based on the Brinkman Index were assessed by the Mann Whitney test with a result of \( p = 0.464 \) which means that the IBs of the two groups were not significantly different.

The effective administration of lycopene showed a significant difference \( (p = 0.001) \) on the decrease in plasma IL-8 levels in the pre-post treatment group, and in the pre-post control group \( (p = 0.001) \). The difference in changes in IL-8 levels (pre-post) between the treatment and control groups showed a statistically significant \( p = 0.029 \) as listed in table 2.

The effective administration of lycopene showed a significant difference \( (p = 0.001) \) to the hospitalization time in the pre-post treatment group; as well as in the pre-post control group \( (p = 0.000) \) as listed in table 3.

**Discussion**

The Indonesian Lung Doctors Association in 2016 and GOLD 2017 said the prevalence of COPD sufferers was predominantly in the male sex associated with smoking and exposure to harmful gases or air pollution outside the home.3

The mean age in the treatment group was \( 65.12 + 8.94 \) years and \( 67.18 + 9.99 \) years in the control group.10 Prevalence based on age according to PDPI 2016 and GOLD 2017 will increase with age and the highest is found at age\( > 60 \) years.11 Age is a risk factor for COPD because it is associated with aging as a result of cumulative exposure during the life of the respondent. The prevalence and mortality of COPD tend to be higher in men than in women. But in developing countries, the prevalence of COPD occurs equally in men and women, this is related to changes in tobacco smoke patterns.12 The education level of respondents in the treatment and control groups ranged from elementary school to junior high school education.

The level of work of the majority of respondents were farmers in the treatment and control groups. The level of education and employment history describes the socioeconomic status. The socioeconomic level as a risk factor for COPD can not be done with certainty but plays a role in understanding smoking habits, exposure to
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hazardous substances, and compliance with medication that will have an impact on one's health behavior. Respondent characteristics based on body mass index (BMI) assessed using the Mann Whitney test obtained \( p = 1.000 \) so that the BMI of the two groups did not differ significantly. The results of previous studies showed that the BMI of COPD patients in Sragen Regional General Hospital majority of BMI is normal.

Cigarette smoke, pollution exposure inside and outside the room, dense settlements, and poor nutrition are risk factors for COPD. Cigarette smoke is a cause of respiratory symptoms and impaired lung function with a high prevalence. The more number of cigarettes smoked and the longer the smoking habit, the higher the risk of suffering from COPD. Passive smokers with repeated exposure, exposure to environmental pollutants, and particles in the workplace are also predilections of COPD. The degree of exacerbation was assessed by the Mann Whitney test with \( p = 0.720 \), so the degree of exacerbation between the treatment and control groups was not significantly different.

Exacerbation of COPD causes an increase in the inflammatory response of the nasal tract which contributes to worsening clinical symptoms, pulmonary function, quality of life, and increased mortality. COPD can occur due to complex interactions between genes and the environment. Cigarette smoke as a risk factor for COPD even in heavy smokers has a chance of COPD. Genetic factors, namely sex, history of the disease also affect the risk of COPD. In general, men have a higher risk than women because it is associated with smokers, which generally occurs in men. The level of individual susceptibility to infection has an effect on the occurrence of COPD exacerbations including HIV infection and tuberculosis as comorbidities that can increase the risk of COPD. Besides the environmental factors that influence COPD are occupational type, environmental exposure, and socioeconomic status related to BMI / Body Mass Index. Environmental exposure that occurs as a result of work includes organic or inorganic dust, chemical agents, and smoke. Genetic risk factors are associated with a hereditary deficiency of alpha-1 antitrypsin (AATD), as a major circulating inhibitor of a serine protease. Although AATD deficiency occurs in only a small proportion of the world's population, this illustrates the interaction of genes with environmental exposure as a predisposing factor in COPD individuals.

The pathogenesis of COPD is related to the process of an inflammatory response in the airways to irritants including cigarette smoke. Inflammation of the lungs due to autoantigen and lung microbiome disorders as similar to other chronic diseases. Pathogenesis factors that influence COPD are oxidative stress such as cigarette smoke and inhaled particles can reduce antioxidants which can reduce levels of transcription nuclear factor-erythroid 2 related factor 2 (Nrf2) which is responsible for the regulation of many antioxidant genes. Another factor is the protease-antiprotease imbalance. Protease breaks down connective tissue components and antiproteases play a role in balancing the work of proteases. Increased protease levels originate from epithelial cells and inflammatory cells in COPD patients. Protease mediates the destruction of elastin; as a component of connective tissue in lung parenchyma.

COPD is characterized by an increase in the number of macrophages, neutrophils and lymphocytes (Tc1, Th1, Th17 and ILC3) in the respiratory tract, lung parenchymes. In some patients such as asthma there is also an increase in eosinophils, Th2 or ILC2. This will have an impact on the release of multiple inflammatory mediators so that they attract inflammatory cells (chemotactic factor), strengthen the inflammatory process (proinflammatory cytokines) and induce structural changes (growth factor).

Exacerbation of COPD is an acute condition characterized by worsening of respiratory symptoms and daily variations in normal symptoms that require changes in therapy. Exacerbations are often found in COPD patients caused by bacterial or viral infections causing an increase in the inflammatory response,
environmental pollution, and other unknown factors. COPD exacerbations will be characterized by three cardinal signs, namely increased breathlessness, increased sputum production, and changes in the color of the sputum to purulent. COPD exacerbations can occur due to interactions between host factors, bacterial or viral infections, and environmental changes that can increase airway inflammation, which is the cause of mucous hypersecretion, airway constriction, and alveolar destruction. *Haemophilus influenzae* and *Streptococcus pneumoniae* are the main microorganisms that cause exacerbations in COPD. *Haemophilus influenzae* will cause direct damage to the epithelium and endotoxin produced will result in an increase in proinflammatory cytokines namely IL-6, IL-8, and TNF-α.²¹

Interleukin-8 is the strongest chemo-practice that triggers neutrophil chemotaxis and plays an important role in the inflammatory process in COPD exacerbations. The use of currently available anti-inflammatory is considered not effective enough because most cases of COPD are resistant to glucocorticoids due to damage to histone deacetylase2 (HDAC2) due to exposure to cigarette smoke and oxidative stress.⁵ Interleukin-8 can induce neutrophils to leave blood vessels, and migrate to tissues. Interleukin-8 is produced by monocytes, neutrophils, T cells, endothelial cells, and epithelial cells after exposure to antigen.²² Cigarette smoke can stimulate the release of IL-8 from bronchial epithelial cells thereby increasing levels of IL-8. Increased IL-8 production can also be caused by the activation of pro-inflammatory cytokines, microbes, and their products.²³

Lycopene belongs to the carotenoid group which has fat-soluble properties with red pigments, found mostly in tomatoes, and has a positive effect on the respiratory system; which can function as an anti-inflammatory in COPD.⁶ Lycopene will inhibit the activation of NF-κB resulting in a decrease in IL-8 levels in patients with acute exacerbation of COPD.²³ The production of proinflammatory cytokines is suppressed by inhibiting activation of nuclear factor kappa beta (NF-κB) which is an important transcription factor in the inflammatory process and controlling the production of NF-β activation through the process of translocation and phosphorylation of NF-κB / p 65 β β kinase inhibitors (IKK) α and IKK β which then cause transcription of the IL-8 inflammatory gene.²⁴ Lycopene, is a class of carotenoids with 11 conjugated double bonds that have anti-inflammatory properties through their antioxidant activity. Lycopene can inhibit tumor necrosis factor α (TNFα) adhesion stimulated by monocytes to endothelial cells and suppress the expression of intercellular cell adhesion molecule-1 (ICAM-1) at the transcription level. In addition, lycopene can have an inhibitory effect by inhibiting the degradation of the inhibiting protein, IκBa, in the pretreatment process. Lycopene can increase intracellular glutathione (GSH) levels and glutamate-cysteine ligase expression. Lycopene is able to suppress the activation of TNFα signaling pathways through increased expression of HO-1 mediated by Nrf2.²⁵ Until now there has been no research on the effect of lycopene on IL-8 levels in patients with acute exacerbation of COPD.

Exacerbation of COPD is characterized by increased oxidative stress and the release of inflammatory mediators. Giving lycopene will inhibit the activation of NF-kB so that there is a decrease in the production of proinflammatory cytokines, IL-8. This inhibition will result in decreased airway inflammation and mucus hypersecretion thereby reducing airflow obstruction and accelerating the recovery of symptoms of COPD exacerbations.²⁶ The limitations of the study are the limitations that are not distinguished causes of exacerbations of infection or non-infection and other basic comorbidities.

**Conclusion**

The effect of administration lycopene 10 mg per day can reduce IL-8 levels and hospitalization time in patients with acute exacerbation of COPD.
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