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The Effect of Ginseng Extract on Serum Interleukin-6 Levels in Patients with Community-Acquired Pneumonia

Fachrurrodji, B. Rina A. Sidharta, Dian Ariningrum, JB. Suparyatmo, MI. Diah Pramudianti

Department of Clinical Pathology, Faculty of Medicine, Sebelas Maret University/Dr. Moewardi Hospital, Surakarta, Indonesia.
E-mail: fachrurrodji80@gmail.com

ABSTRACT

Community-Acquired Pneumonia (CAP) is the most common cause of death and illness in the world. Increased IL-6 can be used as an early indicator of infection or inflammation. Ginseng is a popular herbal medicine. The anti-inflammatory effect of Ginseng is mediated by its ability to inhibit Nuclear Factor Kappa Beta (NF-kB), a proinflammatory regulator to initiate the synthesis of cytokines TNF-α, IL-1β, IL-6, and IL-8. Clinical trial research, quasi-experimental design with a pretest-posttest approach was carried out on 26 community pneumonia patients who were hospitalized at Dr. Moewardi Hospital, Surakarta from October 2020 to January 2021 using purposive sampling. The independent variable was Ginseng extract (GinsanaR) at a dose of 2x100 mg and the dependent variable was serum IL-6 levels. Serum IL-6 levels were measured using the Sandwich Enzyme-Linked Immunoabsorbent Assay (ELISA) method. Mean IL-6 levels in the control group on day 0, day 3, and day 14 were 232,89+156,61 pg/mL, 113,46±83.30 pg/mL and 66.18±66.02 pg/mL, respectively (p=<0.001). Mean IL-6 levels in the treatment group on day 0, day 3, and day 14 were 519,55±609,19 pg/mL, 205.41±329.17 pg/mL and 133,59±291,68 pg/mL, respectively (p=<0.001). Delta IL-6 levels in the control group and the treatment group on day 3 compared to day 0, the mean of the IL-6 control group -119,42±111,70 pg/mL, the mean for the IL-6 treatment group -314,14±532,16 pg/mL; On day 14 compared to day 0, the mean of the IL-6 control group was -166,70±135,54 pg/mL, the mean of the IL-6 treatment group was -385,96±547,10 pg/mL; On day 14 compared to day 3, the mean IL-6 control group was -47.28±47.47, the mean IL-6 control group was -71.82±58.16. The post hoc test (Wilcoxon) obtained a p-value < 0.05, suggesting that Ginseng extract has a significant effect on reducing serum IL-6 serum levels in community pneumonia patients.

Keywords: Community-acquired pneumonia, Ginseng, IL-6

INTRODUCTION

Lower respiratory tract infection is one of the main causes of morbidity and mortality, leading to 34-60% of deaths from a total of 3,941,000 deaths worldwide. Pneumonia is an acute infection or inflammation of the parenchyma or lung tissue caused by bacteria, viruses, fungi, or parasites. Community-Acquired Pneumonia (CAP) is a lung infection that is acquired by patients outside the hospital or in the community. Community-acquired pneumonia can be caused by bacteria, fungi, parasites, or viruses and causes death and remains the highest cause of death and disease worldwide.[1-3]

The global mortality rate for CAP is estimated at 1.4 million annually. A prospective study of 25,000 males in the United States concluded that CAP patients aged over 65 years had a 4.17 times higher risk of mortality compared to those under 45 years of age. Community-acquired pneumonia is included in the top ten cases of hospitalization in Indonesia. The distribution of patients was balanced between the two genders with 53.95% cases found among male patients and 46.05% cases found among female patients. The CAP case has a Crude Fatality Rate (CFR) of 7.6% and remains the highest. In 2019 there were 225 cases of CAP who were hospitalized at the Dr. Moewardi Hospital, Surakarta. Based on the data of Basic Health Research (RISKESDAS), the prevalence of pneumonia in 2018 and 2013 based on the diagnosis of health workers was approximately 2.0% and 1.8%, suggesting an increase of 2%.[3-6]

The mechanism of exacerbation in CAP cases involves various inflammatory factors. In the early stages of pneumonia, alveolar macrophages produce a variety of inflammatory cytokines and chemokines, which attract and activate polymorphonuclear leukocytes and promote an appropriate immune response in the lung parenchyma. In addition, increased production of TNF, IL-1, IL-6, IL-8, IL-12, and IFN-γ was found in the blood circulation of patients with CAP.[7]

Human IL-6 consists of 212 amino acids, including the amino acid peptide and the gene mapped to chromosome 7p21. Although the core protein is 20 kDa, glycosylation accounts for a size of 21–26 kDa at IL-6. The terminal half-life of IL-6 was 15.5 hours measured at the initial stage after peak concentration, from 12 to 18 hours after inflammatory stimulation. Interleukin-6 is one of the cytokines released by macrophages, which is activated by the acute phase response contributing to host defense. One of the advantages of the IL-6 measurement test compared to CRP and PCT is its rapid response to infection. Another diagnostic benefit of IL-6 over PCT is its higher sensitivity as a biomarker of localized infection. Several studies have suggested that IL-6 is a predictor of treatment failure or death. The physiological concentration of IL-6 in human serum is relatively low (1-5 pg/mL). Concentrations increase rapidly in response to infection, trauma, injury, and extreme situations. Increased concentrations of IL-6 can be used as an early indicator of infection or inflammation and are integrated with host immunological defenses. Studies in IL-6-deficient mice have confirmed that IL-6 is required for host immunity to antimicrobials. These outcomes are frequently reported in humans. Interleukin-6 is classified as a lymphokine, a cytokine that affects the survival, proliferation, differentiation, and effector of T cells and B cells. These properties often help to distinguish the biological activity of IL-6 from TNF-α.[8,9] Ginseng is a perennial plant that has been used as a popular herbal medicine. The taxonomy of Panax Ginseng is as follows: kingdom: Plantae, division: Angiosperms, subdivision: Eudicots, class: Asterids, order: Apiales, family: Araliaceae, subfamily: Araliodeae, genus: Panax, species: Ginseng. Panax species: Burkill notoginseng (Chinese Ginseng/Tienchi), Panax Ginseng C.A. Meyer (Korean Ginseng), Panax Japonicus C.A. Meyer (Japanese Ginseng), and Panax quimquefolius L (American Ginseng). There are 13 plants related to the Panax genus, 5 of which are used for medicine, such as Panax Ginseng, American Ginseng, Vietnamese Ginseng, Japanese Ginseng, and Pseudoginseng. Of the five Ginsengs, Panax Ginseng is the most widely used for treatment; it has been used in 16.6% of the 3,944 prescriptions, as reported by the Korean Clinical Pharmacopoeia.[10] The pharmacological effect of Ginseng comes from its various active ingredients such as ginsenoside, polysaccharides, peptides, phytosterols, polyacetylenes, polyacetylinic alcohols, and fatty acids. Ginseng has been recognized as an immune modulator. The roots, stems, leaves, and extracts have been used to maintain immune homeostasis and strengthen resistance to disease or microbial infection.[11] Ginsenoside is the main pharmacologically active component of Ginseng. Ginsenosides, also known as steroid-like saponins, are typical of the Ginseng species. There are more than 100 ginsenosides. Based on the type of its chemical structure, ginsenoside is divided into 4 groups.[12,13]

This study aimed to analyze the effect of Ginseng extract on serum IL-6 levels in CAP patients by measuring serum IL-6 levels using the sandwich Enzyme-Linked Immunosorbent Assay (ELISA) method with ELISA microplate reader Rayto and the detection range interval of 0-50 pg/mL.

The biomedical research Ethics Committee approved this study of Sebelas Maret University, Faculty of Medicine/RSDM in Surakarta, recommendation number 1.298/XII/HREC/2020.

METHODS

This study used a pre-post-test quasi-experimental design, which was carried out at the Clinical Pathology Installation of the Dr. Moewardi Hospital in Surakarta from October 2020 to January 2021. The sample of this study were bacterial community pneumonia patients who were hospitalized at Dr. Moewardi and controls to the Pulmonary Outpatient Clinic on Sunday. Laboratory tests during the study were performed at the Clinical Pathology Laboratory of Dr. Moewardi Hospital from October 2020 to January 2021. Sampling was carried out by purposive sampling according to inclusion and exclusion criteria. The inclusion criteria used in this study were patients aged over 18 years diagnosed with bacterial community pneumonia and proven by culture results, requiring hospitalization in the usual care room, a patient outcome research team value of 70-130, and willing to participate in the study. Patients with a diagnosis of nosocomial pneumonia, comorbid or immunocompromised conditions such as HIV, chronic renal failure, pregnancy, and heart disease patients who were on warfarin therapy were excluded from this study. Drop-out criteria in this study were complaints of side effects/allergic reactions to Ginseng extract, drug withdrawal, withdrawal, worsening of the condition, or death.

Randomization and grouping were carried out by dividing the sample into a treatment group and a control group with a ratio of 1:1. The treatment group received standard antibiotics of B-lactam and macrolide with the addition of Ginseng extract 2x100 mg/day for 2 weeks. The control group received B-lactam and macrolide. Informed consent was

given before the study was conducted. The sample may be withdrawn from the study if any side effects are found.

IL-6 levels measured before the therapy were reported as a pre-test (H-0), on day 3 and day 13 as a post-test. Determination of the validity of analytical tests was carried out first before measurement, including tests of analytical precision (accuracy) and analytical accuracy (accuracy); therefore, the quality of the test results can be accounted for. Sampling in both groups was carried out by taking 3 mL (1 tube) blood samples without anticoagulant. Centrifugation was carried out at a speed of 5000-6000 rpm for 15 minutes to separate serum from blood cell components. The serum formed was put in an aliquot that had previously been labeled with an identity with a 100 µL pipette and a disposable tip (yellow color). Then the sample was placed in a sample container and stored in a refrigerator at -80ºC until the sample size was sufficient, then the serum IL-6 levels were measured using the sandwich ELISA method. The ELISA microtiter plate in this kit was coated with the human-specific IL-6 antibody. The sample or standard was added to the microplate well, then a specific antibody for human IL-6, avidin-Horse Radish Peroxidase (HRP) conjugate was added to each well and incubated. The free components were removed by washing, then the substrate solution was added to each well. Only wells containing human IL-6, biotinylated antibody, and conjugated avidin-HRP produced a blue color. The enzyme-substrate reaction was stopped by adding a stop solution and the color changed to yellow. Optical Density (OD) was measured by spectrophotometric method at a wavelength of 450±2 nm. The OD value describes the concentration of human IL-6 in the sample. The detection range was 0–50 pg/mL and analytical sensitivity was 0.94 pg/mL.

Characteristic data of research subjects were presented in descriptive form. Baseline variables were described in mean and SD. Shapiro-Wilks statistical test was used to determine the distribution of the data in this study. To determine the mean difference between the control group and the treatment group, an independent T-test was used if it was normally distributed and the Mann-Whitney test was used if the data were not normally distributed. To find out the difference in mean before and after treatment in one group, paired T-test was used if the data were normally distributed and the Wilcoxon test was used if the data were not normally distributed. Data processed using a computer is considered significant if $p < 0.05$ with 95% CI.

RESULTS AND DISCUSSIONS

This study aimed to analyze the effect of Ginseng extract on serum IL-6 levels in CAP patients. A total of 26 subjects in this study were divided into 2 groups consisting of 13 subjects in the treatment and 13 subjects in the control group. There were no research samples that dropped out in this study.

Tests of analytical precision and accuracy were carried out before the measurement. The results of the daily precision test of serum IL-6, and day-to-day precision of WBC and neutrophils showed consistent accuracy over time (Tables 1 and 2). The results of the accuracy test for parameters of WBC and neutrophil were in the range of the control room, with values of d% were 0.015 and 0.09, respectively.

The results of the accuracy test for the parameters of WBC and neutrophil met the range value, with the values of d% being 0.015 and 0.09, respectively (Table 3).

Table 1. Intra-day precision test (within a day)

Parameter	Mean	SD	CV (%)	Maximum CV (%)
IL-6 (pg/mL)	396.85	18.74	4.72	5.4*

Table 2. Inter-day precision test (between days)

Parameter	Mean	SD	CV (%)	Maximum CV (%)
WBC (10^3/uL)	15.65	0.15	0.96	5*
Neutrophils (%)	7.34	0.15	2.04	5*

Table 3. Results of accuracy test

Parameter	Reference Value {mean (2SD)]	Results	Note	d %
WBC (10^3/uL)	15.51(14.58-16.44)	15.65	Met the range value	0.015
Neutrophils (%)	7.23(6.15-8.31)	7.34	Met the range value	0.009

Characteristics of nominal categorical data (gender) of subjects in this study were presented in the distribution of frequencies and percentages (Table 4). Characteristics of ordinal categorical data (smoking and PSI) of subjects in this study were presented in the distribution of frequency and percentage. Characteristics of numerical categorical data (age, BMI, neutrophils, and WBC) of subjects in this study were presented in the mean+standard deviation.

Based on Table 5, the mean of IL-6 levels in the control group on day 0, day 3, and day 14 was 232.89+156.61 pg/mL, 113,46+83.30 pg/mL and 66.18+66.02 pg/mL, respectively (p=< 0.001). The mean of serum IL-6 levels in the treatment group on day 0, day 3, and day 14 was 519,55+609,19 pg/mL, 205,41+329,17 pg/mL and 133,59+291,68 pg/mL, respectively (p=< 0.001).

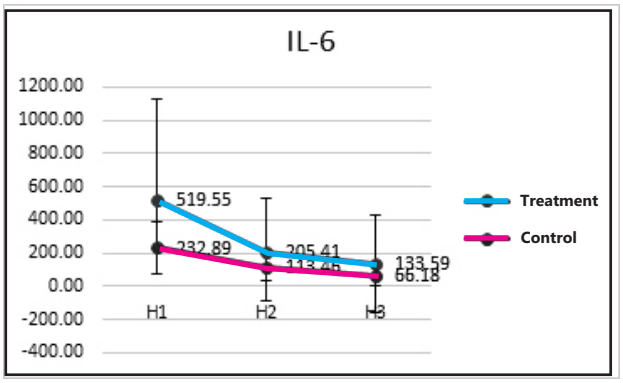

Figure 1. Diagram of difference in serum IL-6 between control and treatment group

The difference in the decrease in serum IL-6 levels in the control and treatment groups can be seen in Figure 1. The results above showed that administration of Ginseng extract as an adjunct

Table 4. Characteristics of research subjects

Characteristics	Group		p
	Control	Treatment	
Gender[a]			0.637
Male	8 (61.5%)	10 (76.9%)	
Female	5 (38.5%)	3 (23.1%)	
Age[b] (years)	55.23±7.26	57.38±10.47	0.548
BMI[b]	18.25±2.57	19.14±2.64	0.394
Smoking[c]			0.825
Yes	5 (38.5%)	6 (46.2%)	
Ex	5 (38.5%)	5 (38.5%)	
No	2 (15.4%)	3 (23.1%)	
PSI[c]			0.354
II	4 (30.8%)	6 (46.2%)	
III	4 (30.8%)	4 (30.8%)	
IV	5 (38.5%)	3 (23.1%)	
Neutrophils[b] (%)	84.21±3.89	86.48±5.76	0.250
WBC[c] (10^3/uL)	18.06±7.66	13.15±5.05	0.144
Bacterial culture[a]			0.540
Klebsiella pneumoniae	4 (30.8%)	5 (38.4%)	
Pseudomonas aeruginosa	3 (23.1%)	1 (7.7%)	
Enterobacter cloacae	1 (7.7%)	1 (7.7%)	
Staphylococcus haemolyticus	2 (15.3%)	3 (23.1%)	
Staphylococcus aureus	0 (0.0%)	1 (7.7%)	
Escherichia coli	0 (0.0%)	1 (7.7%)	
No growth	3 (23.1%)	1 (7.7%)	

Table 5. Difference of serum IL-6 levels between control and treatment group

Group	IL 6 Levels Day 0 0[a] (pg/mL)	IL 6 Levels Day 3[a] (pg/mL)	IL6 Levels Day 14[a] (pg/mL)	p
Control[b]	232.89±156.61	113.46 ±83.30	66.18±66.02	< 0.001[a]
Treatment[b]	519.55±609.19	205.41 ±329.17	133.59±291.68	< 0.001[a]
p-value[b]	0.209	0.817	0.427	

Table 6. Difference of serum IL-6 levels in the control group between day 3 and day 0, between day 14 and day 0, and between day 14 and day 3

Group	Difference		p
	Control	Treatment	
Between day 3 and day 0	-119.42±111.70	-314.14±532.16	0.174
Between day 14 and day 0	-166.70±135.54	-385.96±547.10	0.174
Between day 14 and day 3	-47.28 ±47.47	-71.82±58.16	0.249

therapy in addition to standard therapy was able to reduce serum IL-6 levels and was statistically significant compared to standard therapy. Increased concentrations of IL-6 can be used as an early indicator of infection or inflammation and are integrated with host immunological defenses.

Based on Table 6, the mean decrease of serum IL-6 levels in the control and treatment group between day 14 and day 3 was -119,42+111,70 pg/mL and -314,14 +532,16 pg/mL; the mean decrease of serum IL-6 levels on day 3 in the treatment group was higher than the control group, despite the insignificance (p=0.174). The mean decrease of IL-6 in the control group and treatment group was -47.28+47.47 and -71.82 +58.16, respectively. The difference in serum IL-6 on day 14 compared to day 3 in the treatment group was higher than the control group, despite the insignificance (p=0.249).

Table 7. Post hoc test of difference of serum IL-6 levels between control and treatment group on day 0, day 3, and day 14

Group	p-value	
	Day 3	Day 14
Control		
IL 6 on day 0	0.001*	0.001*
IL 6 on day 3		0.001*
Treatment		
IL 6 on day 0	0.001*	0.001*
IL 6 on day 3		0.001*

Based on Table 7, the comparison of IL-6 levels between day 0, day 3, and day 14 of the post hoc test (Wilcoxon) treatment group obtained a p-value < 0.05, indicating a significant difference in IL-6 levels between day 0, day 3, and day 14. The control group comparison of IL-6 levels between day 0, day 3, and day 14 also obtained a p-value < 0.05, indicating a significant difference in IL-6 levels between day 0, day 3, and day 14.

Pneumonia is an acute inflammation of the lung parenchyma caused by microorganisms (bacteria, viruses, fungi, parasites). Community pneumonia is one of the most common acute infections requiring hospitalization and a cause of high morbidity and mortality worldwide. The diagnosis of pneumonia was made based on anamnesis (history of cough, shortness of breath, fever), physical examination (fever, tachycardia), and confirmed by chest X-ray and laboratory. The use of validated scoring systems and biomarkers such as IL-6 helps determine the severity of pneumonia and guides the decision between outpatient or inpatient.[14]

Community-acquired pneumonia patients in this study were dominated by male subjects (69.23%). These results were following the research of Uranga *et al*. in Spain, which found that 63.3% of males suffered from community pneumonia and were hospitalized.[15] This might be influenced by environmental factors and habits, in which males are more often exposed to smoke from the workplace and smoking habits, which are one of the risk factors for community pneumonia.

Body mass index was relatively the same between the control and treatment groups. There were 8 patients (30.8%) who were underweight. Lack of body weight can be caused by nutritional intake that is not optimal; thereby leading to an unhealthy immune system. The history of smoking between the control group and the treatment group was relatively the same, indicating that 42.30% of patients still smoked. Cigarettes can cause damage to airway cilia, which can disrupt mucociliary clearance and increase the risk of respiratory tract infections. The PSI scores in both groups were relatively the same; however, the difference in PSI scores reflected the severity of community pneumonia suffered by the patient, which could affect the response to therapy.[14,15]

The most common types of bacteria found in both the control and treatment groups were Gram-negative bacteria, such as *Klebsiella pneumoniae*. This was in accordance with data obtained from several hospital institutions in Indonesia and the research of Lin *et al*. in Taiwan, which found that the most common CAP-causing bacteria are Gram-negative bacteria, such as *Klebsiella pneumoniae*.[16-18]

Blood test results showed that there was no significant difference in the percentage of

neutrophils between the control and treatment groups. An increase in WBC count was found in both groups. Cytokines are produced in response to inflammatory reactions that will increase neutrophils, leading to increased leukocyte count.[18]

This study found that there was an increase in IL-6 in all samples before treatment. This was consistent with studies on IL-6-deficient mice, which found that IL-6 is required for host immunity to antimicrobials. These outcomes also often occur in humans. Bacci *et al*. have suggested that elevated IL-6 is a strong predictor of 30-day mortality, with median IL-6 concentrations significantly increased in patients with severe CAP. Mendez *et al*. also demonstrated in their study that IL-6 was an independent predictor of 30-day mortality. Ken *et al*., found high concentrations of serum Tumor Necrosis Factor (TNF), IL-6, IL-8, and interferon (IFN-ɤ) at hospital admission. Interleukin-6 is classified as a lymphokine, a cytokine that affects the survival, proliferation, differentiation, and effector of T cells and B cells. These properties often help to distinguish the biological activity of IL-6 from TNF- α.[8,9,19-21]

A study by Kim *et al*. showed that there was a significant decrease ($p < 0.001$) in IL-6 levels with the administration of Ginseng extract. Iqbal *et al.* stated that Ginseng has a role in inflammatory pathways, such as reducing the production of NF-kB and TNF-α, regulating DNA binding, transcriptional activity, releasing cytokines, regulating intracellular cAMP pathways; decreasing expression and release of TNF-α, IL-6, and IL-8 as well as increasing T cell count and Natural Killer (NK) activity. Research by Sari found decreased IL-8 levels in exacerbating chronic obstructive pulmonary patients. The anti-inflammatory effect of Ginseng is also related to its ability to act as an antioxidant.[12,22]

The heterogenous degree of disease in the study population remains the limitation of this study, making it difficult to determine the effect of this disease degree on clinical improvement and decrease in IL-6 levels. In addition, the number of subjects in this study was too small to stratify based on the degree of disease. The body response of each subject to the infection process and antibiotics in this study was also not considered. The research was only carried out at one center, making it impossible to determine the difference if it was taken place at a different center.

CONCLUSIONS AND SUGGESTIONS

This study showed that administration of Ginseng extract had a significant effect on decreasing serum IL-6 levels in community pneumonia patients. Ginseng extract can be considered as adjunctive therapy in hospitalized CAP patients. Further research is needed with a homogeneous population of CAP according to the degree of disease and conducted at multicentered locations.

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