Original Article

The Effect of Ginseng Extract Supplementation on Procalcitonin Level, Neutrophil, and Length of Stay In Patients With Community Acquired Pneumonia

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Abstract

Background: Pneumonia is an acute inflammation of the lung parenchyma caused by microorganisms (bacteria, viruses, fungi, parasites) and causes of high morbidity and mortality. Ginsenoside in ginseng have anti-inflammatory effects, potentially as adjunctive therapy in community-acquired pneumonia (CAP) patients. As much as 43% of patients at dr. Moewardi Hospital in 2016 were hospitalized have passed away. The aim of this study was to determine the effect of ginseng extract on levels of procalcitonin, neutrophils, and length of stay of community-acquired pneumonia patients.

Method: The quasi-experimental clinical trial with the pretest posttest design approach was conducted on 26 community acquired pneumonia patients who were hospitalized in Dr. Moewardi Hospital Surakarta from October until November 2019 using consecutive sampling. The control group (n=13) received standard antibiotics while the treatment group (n=13) received additional ginseng extract 2x100 mg/day for 14 days. Procalcitonin was measured at admission, third and fourteenth day; neutrophils are measured at admission and third day; length of stay is based on the number of days of treatment in hospital.

Results: There was a significant difference (P=0.001) towards decreased of serum procalcitonin levels between treatment group (-0.63±0.06) compared to control group (-0.38±0.07). There was a significant difference (P<0.001) towards decreased of neutrophil levels between treatment group (-6.68±1.34) compared to control group (-3.51±0.88). There was a significant difference (P=0.001) towards decreased of length of stay between treatment group (5.69±0.95) compared to control group (7.15±0.99).

Conclusion: Ginseng extract containing ginsenoside as its main ingredient, can act as an anti-inflammatory which can be used as adjunctive therapy in community-acquired pneumonia patients who are hospitalized to accelerate clinical improvement and shorten the length of stay.

Keywords: pneumonia, ginseng, procalcitonin, neutrophil, length of stay.

INTRODUCTION

Respiratory tract infections are still a public health problem. They are one of the leading causes of death globally despite advances in diagnostics, antibiotic therapy, and even intensive care.[1] The World Health Organization (WHO) report states that the highest cause of death from infectious diseases in the world is acute respiratory infections, including Pneumonia. Pneumonia is defined as an acute inflammation of the lungs caused by microorganisms (bacteria, viruses, fungi, parasites).[2]

The incidence of community acquired pneumonia (CAP) varies considerably according to age, comorbidities, geographic location, study methods, case definition and study population. A recent study of Asian countries reported that CAP is responsible for 420.5 episodes per 10.000 discharges in Indonesia. Mortality rate in hospitalized patients is 6–20%, but it varies widely according to treatment setting and severity disease, while mortality in primary care and ambulatory patients is less than 1% in most of the population, rising in patients over 65 years. One-nineth of patients hospitalized with CAP will need intensive care unit (ICU) admission and mortality in these patients reaching 50%.[3]

Widmer et al. in Switzerland in 2008 conducted a prospective study of 875 pneumonia patients to determine the factors that influence the length of hospitalization. The size of stay of the patient is influenced by age, the clinical condition of the patient, the need for home care, comorbidities, multi-lobar lung disorders, disease complications, and the severity of Pneumonia characterized by high levels of procalcitonin (PCT), C-reactive protein (CRP), patient risk class based on Pneumonia. Severity Index (PSI), and the need for intensive care.[4]

Antibiotics play an essential role in controlling disease, but irrational use and the presence of mutations in microorganisms cause the elimination of microorganisms to be non-optimal. The use of herbal medicines is increasing and is considered an additional therapy in the treatment of infectious diseases, assuming that they are widely available, more economical, and have minimal side effects so that they are safer to use. The pharmacological effects of natural products, especially their anti-inflammatory and antimicrobial effects, have become an attractive new treatment strategy. Combining natural products with antibiotics can provide a synergistic effect on antibiotics and minimize toxicity.[5–8]

Ginseng is one of the most studied herbal plants, especially in Asia. Ginseng grows well in environments with cool air and dry climates. Ginsenoside is the main active component of ginseng. Ginseng has antimicrobial, anti-inflammatory, and antioxidant properties. Choi et al. in 2012 showed that the aqueous extract of KRG provided anti-bacterial activity against Listeria monocytogenes with an MIC50 of 1.0 mg/mL. Lee et al. used 0.2% ginseng extract to induce cell morphological damage and loss of structural integrity of the bacterial cell wall.[9,10] And TNF- through

inhibition of the mitogen-activated protein kinases (MAPK) pathway and nuclear factor kappa – light chain enhancer of activated B cells (NF–κB).[11,12]

This study aims to determine the effect of giving ginseng as an anti-inflammatory in pneumonia patients. Researchers hope to prove the role of ginseng as an adjunct therapy in improving symptoms and shortening patients' length of stay. Markers of decreased inflammatory reactions will be measured by reducing procalcitonin and neutrophils in the blood.

METHOD

Community acquired pneumonia is an acute inflammation of the lung parenchyma that is acquired in the community. Community acquired pneumonia is associated with high and variable mortality rates among hospitalized patients. The ability to assess prognosis of people with CAP is very important. Accurate assessment of prognosis may help physicians make clinical decisions about hospitalization and management. The clinical prediction rule for CAP patients called the pneumonia severity index (PSI). The PSI is a clinical prediction rule that can be used to predict the need for hospitalization, calculate the probability of morbidity and mortality among patients with CAP.[2]

Empirical therapy for CAP patients is a respiratory fluoroquinolone such as Levofloxacin or Moxifloxacin, or β-lactam plus a macrolide. Discharge criteria for patients with community acquired pneumonia is if clinically stable. Clinically stable criteria are able to eat and drink, temperature ≤37.8°C, respiratory rate ≤24/min, pulse rate ≤100/min, oxygenation saturation ≥90% or PO_2 ≥60mmHg, white blood cell count $<12\times10^9$/L, dan the comorbidities are stable.[2]

This research is a clinical trial using the Quasi Experimental method and a pre-test and post-test design. The research was conducted at Dr. Hospital Moewardi Surakarta in October 2019. The study population was community pneumonia patients undergoing treatment at RSUD Dr. Moewardi Surakarta in October 2019. Sampling was done by the consecutive selection, namely selecting topics based on predetermined characteristics.

The inclusion criteria for this study were community pneumonia patients aged more than 18 years, hospitalized in an ordinary room, willing to participate in the survey, PORT value 51–130. Exclusion criteria were nosocomial Pneumonia had comorbid or immunocompromised conditions (HIV, chronic kidney failure, pregnancy), heart disease patients on warfarin therapy. The drop out criteria included patients who died during follow-up, resigned, severe side effects during the study, and patients lost to follow-up (not control at post-test).

Data analysis was performed with SPSS 21 for Windows. Statistical test to determine the distribution or distribution of data using Shapiro Wilk and Kolmogorov Smirnov. Test the difference between the control and treatment groups with an independent T-test or

Mann Whitney test. Different tests before and after treatment using pair T-test or Wilcoxon test.

RESULTS

This research was conducted on community pneumonia patients hospitalized at Dr. Moewardi. The total number of samples that met the inclusion criteria and were willing to participate in the study were 30 patients, 4 patients entered the discontinuous criteria, so the number of samples at the end of the study was 26 patients. The research sample was divided into 2 groups: the control group and the treatment group. The control group was only given standard therapy with antibiotics, while the treatment group was given standard treatment plus ginseng extract. Each group consisted of 13 community pneumonia patients.

The essential characteristics of the study subjects are shown in Table 1. The vital parts of the patients included gender, age, body mass index (BMI), smoking history, previous treatment history, Pneumonia Severity Index (PSI) score and bacterial culture.

Table 1. The Characteristics of Study Subjects

Characteristics	Group		P
	Control	Treatment	
Gender[2]			1,000
Male	9 (69,2%)	10 (76,9%)	
Female	4 (30,8%)	3 (23,1%)	
Age[1]	57,08±8,72	59,38±11,00	0,559
BMI[1]	18,37±2,64	19,14±2,64	0,467
Smoking history[2]			1,000
Smokers	6 (46,1%)	5 (38,4%)	
Ex-smokers	3 (23,1%)	4 (30,8%)	
Non-smokers	4 (30,8%)	4 (30,8%)	
Previous treatment history (90 days) [2]			1,000
Yes	11 (84,6%)	8 (61,5%)	
No	2 (15,4%)	5 (38,5%)	
PSI Score (Pneumonia Severity Index)			0,654
II	4 (30,8%)	6 (46,2%)	
III	4 (30,8%)	4 (30,8%)	
IV	5 (38,5%)	3 (23,1%)	
Bacterial cultur[1]			0,540
Klebsiella pneumoniae	5 (38,4%)	4 (30,8%)	
Pseudomonas aeruginosa	1 (7,7%)	3 (23,1%)	
Enterobacter cloacae	1 (7,7%)	1 (7,7%)	
Staphylococcus haemolyticus	3 (23,1%)	2 (15,3%)	
Staphylococcus aureus	1 (7,7%)	0 (0,0%)	
Escherichia coli	1 (7,7%)	0 (0,0%)	
No growth	1 (7,7%)	3 (23,1%)	

Notes: [1]Different test is done by T-test; [2]Different tests were performed using chi-square/fhiser exact test; PSI scores (ordinal data) were performed using the Mann Whitney test.

Gender characteristics of the 30 research subjects, 19 subjects (63%) were male, with the mean age of the control and treatment groups being 57.08±8.72 years and 59.38±11.00 years. The average body mass index in the control and treatment groups was 18.37±2.64 and 19.14±2.64. The characteristics of smoking status in the control group were 6 patients (46.2%) still smoking, 3 patients (23.1%) ex-smokers, and 4 patients (30.8%) not smoking. Subjects who still smoked in the treatment group were 5 patients (38.4%), 4 patients (30.8%) used to smoke, and 4 patients (30.8%) who did not smoke.

Characteristics of previous treatment history in the control group showed that 11 patients (84.6%) had been treated previously, and 2 patients (15.4%) had no previous treatment history. In the treatment group, 8 patients (61.5%) had been treated previously, and 5 patients (38.5%) had no previous treatment history. Most of the bacteria that caused pneumonia in the control and treatment groups were Klebsiella pneumonia, namely 5 patients (38.5%) in the control group and 4 patients (30.8%) in the treatment group.

The basic characteristics of the research subjects based on the results of the homogeneity analysis showed that almost all qualitative/categorical and quantitative/numerical variables had values that were not significantly different between the control and treatment groups. This indicates that the samples in both groups are homogeneous and meet the experimental feasibility rules.

Table 2 shows the effect of giving ginseng extract on neutrophil levels. The decrease in neutrophil levels in the control group was 3.51±0.88; while in the treatment group, it was 6.68±1.34. Decreased serum neutrophil levels in the treatment and control groups obtained P<0.001, meaning that the control and treatment groups experienced a significant decrease in serum neutrophil levels. However, the reduction of neutrophil levels was greater in the treatment group. It was statistically significant (P<0.001) so that the administration of ginseng extract effectively accelerated the decrease in serum neutrophil levels.

Table 3 shows the effect of giving ginseng extract on procalcitonin levels. The decrease in PCT levels on the third day compared to the initial PCT in the control and treatment groups was 0.38±0.07 and 0.63±0.06, respectively. The decrease in PCT levels on the fourteenth day compared to the initial PCT in the control and treatment groups was 1.36±0.53 and 1.43±0.56, respectively.

Different tests before and after treatment in the control group obtained P=0.001. In contrast, the treatment group got value of P=0.001, which means that both the control and treatment groups experienced a significant decrease in PCT levels.

The decrease in PCT on the third day in the treatment group was greater than in the control group. The administration of ginseng extracts effectively accelerated the decrease in PCT levels.

Table 2. Different test of serum neutrophil levels between the control group and the treatment group

Group	Neutrofil (%)			
	Day-0	Day- 3	P	Difference
Treatment	86,48±5,76	79,81±4,98	<0,001 [b]	-6,68±1,34
Control	84,21±3,89	80,71±3,81	<0,001 [b]	-3,51±0,88
P	0,250[a]	0,610 [a]	-	-

Notes: [a]different test with independent t test; [b] Test different premises Pair t test.

Table 3. Different test of Procalcitonin levels between the control group and the treatment group

Group	*Procalcitonin* (PCT)					
	Day-0	Day-3	Day-14	P	Δ day 3 – 0	Δ day 14 – 0
Control	1,45±0,55	1,07±0,53	0,08±0,03	<0,001[c]	-0,38±0,07	-1,36±0,53
Treatment	1,49±0,57	0,86±0,54	0,06±0,02	0,001[d]	-0,63±0,06	-1,43±0,56
P	0,852[a]	0,200[b]	0,007[b]	-	-	-

Notes: [a]different test is carried out with the Independent t test; [b] Differential test was performed with Mann Whitney; [c]Test the difference is done by Pair t test; [d]A different test was carried out with the Wilcoxon test.

The decrease in PCT levels on the fourteenth day in the control group was not much different from the treatment group and not statistically significant.

Table 4. Test for different lengths of stay in the control group and the treatment group

Variable	Group		P
	Control (n=13)	Treatment (n=13)	
Length of Hospitalization (days)	7,15±0,99	5,69±0,95	0,001

Note: Different test using Independent t test.

Table 4 shows the effect of giving ginseng extract on the length of stay of community pneumonia patients. Patients' average length of stay in the treatment group was 5.69±0.95 days, shorter than the control group, which was 7.15±0.99 days.

The different tests of the control and treatment groups showed P=0.001, which means that there was a significant difference in length of stay between the control group and the treatment group. These results indicate that administration of ginseng extract effectively shortens the length of stay of community pneumonia patients.

DISCUSSION

Pneumonia is an acute inflammation of the lung parenchyma caused by microorganisms (bacteria, viruses, fungi, parasites). Community pneumonia is pneumonia acquired in the community or outside of a hospital. Community pneumonia is one of the most common acute infections requiring hospitalization and a cause of high morbidity and mortality worldwide.[2]

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 procalcitonin helps determine the severity of pneumonia and guides outpatient or inpatient decisions. Proper administration of antibiotics is essential to prevent the worsening of pneumonia patients and shorten the length of treatment. Antibiotic treatment is not always effective in sterilizing the entire respiratory system, so the use of additional drugs for pneumonia has been widely

developed, especially in patients with a history of recurrent infectious diseases and patients with comorbidities.[13–15]

Ginseng is an herbal plant commonly found in Asia with the main content of ginsenoside. Ginsenoside has an anti-inflammatory effect by inhibiting the interaction of LPS with TLR4 on macrophages, inhibiting TNF- production due to LPS stimulation, inhibiting NF-B signaling activation, and inhibiting IL-8 production. Ginsenoside can also suppress TLR2 expression, thereby inhibiting the production of IL-2 and IFN-γ. Giving ginseng extract to the treatment group is expected to reduce serum neutrophil levels procalcitonin and shorten the length of hospitalization.[9,16,17]

Giving ginseng extract on serum neutrophil levels was seen from the decrease in serum neutrophil levels on the third day compared to the initial arrival, both in the control and treatment groups. The reduction in serum neutrophils in the treatment group was greater than the control group and was statistically significant ($P<0.001$). This study showed that standard therapy plus administration of ginseng extract could reduce serum neutrophil levels in community pneumonia patients, with a significant difference compared to the control group.

The interaction of specific microbial adhesins with cellular receptors causes the activation of the transcription factor NF-B, producing various pro-inflammatory cytokines or chemokines (IL-1β, IL-6, IL-8, IL-17, IL-18, and TNF-α). Pro-inflammatory cytokines activate the vascular endothelium, making chemoattractant that allow trans-endothelial migration of neutrophils and acute-phase reactants. Standard therapy, namely antibiotics, caused the decrease in serum neutrophil levels in the control group. Giving antibiotics can affect a person's immune system. Antibiotics can reduce the release of cytokines, thereby reducing the migration of neutrophils to the site of infection, inhibiting the synthesis of pro-inflammatory cytokines and chemokines, and facilitating the release of anti-inflammatory cytokines.[14,18–20]

Another way antibiotics reduce the number of neutrophils is to decrease granulopoiesis and induce antibodies against the formation of haptens in neutrophils. The decrease in serum neutrophil levels in the treatment group given standard therapy plus ginseng extract resulted in a more significant reduction in serum neutrophil levels than the control group, presumably due to a synergistic effect between the two. The bactericidal activity of ginsenoside disrupts the potential membrane integrity of bacterial cells, inhibiting DNA mutagenesis, anti-quorum sensing, anti-adhesive activity, inhibiting pathogen-induced hemagglutination, and modulating the immune system.[14,18–20]

This study showed that Klebsiella pneumonia was the dominant pathogen of CAP cases in Dr Moewardi Hospital. This can be caused by infection with Klebsiella pneumonia which is endemic in Surakarta. Other risk factors that may be responsible for the high bacteremia of Klebsiella

pneumonia are older age, underlying chronic lung disease, patients with severe clinical conditions, immunocompromised patients, and previous medical history.[21]

Luan et al's research at Shijitan Hospital, Beijing in 2017 found that Klebsiella pneumonia was the main cause of adult CAP cases (27.4%). The results of the pathogenic bacterial profile at Dr M. Djamil Hospital, Padang in 2016 by Narlis et al, found that 55.23% of CAP patients were caused by Klebsiella pneumonia. Assefa et al obtained sputum cultures of CAP patients in Gondar, Ethiopia as much as 31% caused by Klebsiella pneumonia. In contrast to the results of the study above, Costa et al found that 45.7% of CAP patients admitted to the Northern Portugal University Hospital were caused by Streptococcus pneumoniae. Sputum culture results of CAP patients at the referral hospital in Hiwot, Northwest Ethiopia 35.9% were caused by Streptococcus pneumoniae.[21–25]

The results of this study are like those of a 2008 study conducted by Song et al. in Denmark, who reported fewer macroscopic lung abnormalities (P=0.0003) and a lower percentage of PMN from bronchial lavage (P=0.0006) in *P. aeruginosa* - infected rats. And given an injection of ginseng extract, 2mg/kgBW for 2 weeks compared to the control group. Research by Nguyen et al. in 2015 in Korea on mice infected with S. pneumoniae and given ginseng extract 100mg/kgBW for 15 days found a decrease in TNF-α, IL-1β levels, decreased TLR-4 receptors, and neutrophil infiltration 48 hours after infection.[20]

Serum procalcitonin (PCT) levels on the third and fourteenth days compared to the initial presentation decreased in the control and treatment groups. The decrease in serum PCT on the third day in the treatment group was greater than in the control group and was statistically significant (P<0.001). In contrast, the decrease in serum PCT on the fourteenth day in the treatment and control groups was not significantly different. The difference in decline was not statistically significant (P=0.758).

From these results, it can be concluded that administration of ginseng extract as an adjunct therapy in addition to standard treatment was able to reduce PCT levels and was statistically significant compared to standard treatment. Empirical antibiotic therapy for community pneumonia patients at RSUD Dr. Moewardi was adjusted to the bacterial pattern of the hospital, where fluoroquinolone antibiotics (Levofloxacin, Ciprofloxacin) or -lactams (Ampicillin, Cefoperazone) plus macrolides (Clindamycin, Azithromycin) were shown to be effective in reducing serum PCT levels in pneumonia patients.

Procalcitonin is a pro-peptide precursor to calcitonin. Procalcitonin is regulated in response to microbial toxins and bacterial-specific pro-inflammatory mediators such as IL-1β, IL-6, and TNF- and PCT levels decrease as pro-inflammatory mediators decrease during recovery. The average physiologic level of PCT in serum is less than 0.1 ng/ml, increasing hundreds of times in systemic bacterial infections. Procalcitonin is not a

marker in the very early phase of disease because levels only increase between 2 and 6 hours after infection, peak in 6 to 24 hours, decrease slowly over 48-72 hours, and persist for several days in the blood in the presence of systemic infection. PCT levels generally fall below 1 ng/ml (or 1 g/l) within 48 hours without infection, indicating the importance of repeat PCT measurements. Serial measurements of PCT over time are informative, and absolute trendlines are more valuable than percentage declines from baseline.[26,27]

The results of this study showed that the decrease in PCT levels on the third day in the treatment group was much greater than the control group. Giving antibiotics can reduce the release of pro-inflammatory cytokines so that PCT levels in the blood will decrease. Giving standard therapy plus ginseng extract was able to reduce procalcitonin levels more than the group that only received standard therapy. This could be due to the synergistic effect between antibiotics and ginseng extract, thereby accelerating the decrease in serum PCT levels.[7,10,28]

Giving ginseng extract was able to inhibit the activity of NF-kB so that it would inhibit the production of pro-inflammatory cytokines. Panax ginseng can increase the phagocytic activity of macrophages and NK cells. Activation of the immune system can be through the formation of TLR complexes, thereby inhibiting the production of pro-inflammatory cytokines and preventing sepsis. The decrease in PCT levels on the fourteenth day in the treatment group and the control group did not differ much, this could be related to the PCT half-life in the blood so that PCT levels had decreased along with the decrease in systemic infection after therapy.[7,10,28]

The results of this study are similar to a study conducted by Hong et al in 2011 which showed that administration of a low concentration of 0.25% ginseng extract could reduce biofilm formation in vitro, increase motility and reduce clustering of Pseudomonas aeruginosa. Staphylococcus aureus significantly reduced bacterial colony formation in the bloodstream, spleen and kidney, which may correlate with bactericidal activation of macrophages. Ginseng pre-treatment can reduce levels of IL-1β, IL-6, IL-12, IL-18, TNF-α, and IFN-γ.[9,10]

A 2008 study by Sung et al. in Korea compared the administration of standard antibiotics with a combination of antibiotics and saponins from ginseng extract against MRSA bacterial cultures. The combination of ginseng extract with kanamycin against MRSA bacteria showed a synergistic or additive effect with a fractional inhibitory concentration (FIC) index value of 0.375–0.75 while the combination of ginsenosides and cefotaxime had an additive effect on MRSA with an FIC index value of 0.625.[29–31]

Ahn et al.'s 2005 study in Korea on 12 rats injected with S. aureus intraperitoneally. Administration of ginseng extract was able to increase survival and reduce the burden of bacteria in the blood during sepsis in mice infected with S. aureus. The combination of ginseng extract and vancomycin gave a higher survival rate

than the administration of each treatment.[20,28]

The results showed that the length of stay for community pneumonia patients in the treatment group was shorter than the control group and was statistically significant with P<0.001. The hope of giving ginseng extract to community pneumonia patients is that it can help reduce symptoms, accelerate clinical improvement, thereby shortening the length of stay of patients.

In this study, there was a significant difference in length of stay between the control and treatment groups, this could be due to the administration of antibiotics plus ginseng extract that could modulate the immune system, inhibit NF-B activity, and decrease the production of pro-inflammatory cytokines. This reduction in systemic inflammatory reactions will accelerate the patient's clinical improvement so that it will shorten the length of stay for pneumonia patients.

Similar results were obtained from a study conducted by Scaglione et al on 75 chronic bronchitis patients. All patients received 875 mg of amoxicillin and 125 mg of clavulanic acid twice daily for 9 days. Patients were divided into two groups, the first group received only antibiotic therapy and the second group was added with 100 mg of standardized ginseng extract (G115®) twice a day. The results showed that the elimination of bacteria and clinical improvement in the second group was faster than the first group, with an average time of 5.9 days and 6.7 days. Patients are considered cured and can be discharged after reducing or even disappearing symptoms of infection, such as coughing, shortness of breath, wheezing, fever, vital signs within normal limits and good oral intake.[12]

There has been no previous study on the effect of ginseng extract on PCT levels, serum neutrophils, and length of stay at the same time, so the results cannot be compared with other studies. Previous studies regarding the administration of ginseng extract have been conducted on patients with chronic bronchitis, cystic fibrosis patients, and patients infected with the influenza virus. The results showed a decrease in inflammatory cytokines, increased phagocytosis and clearance of microorganisms thereby accelerating the clinical improvement of patients.[9,12]

CONCLUSION

The administration of ginseng extract at a dose of 2x100 mg/day can be given as an adjunctive therapy in hospitalized community pneumonia patients to accelerate clinical improvement and shorten the length of stay of patients.

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