Short Communication

Effectiveness of *Zingiber officinale* to reduce inflammation markers and the length of stay of patients with community-acquired pneumonia: An open-label clinical trial

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Abstract

Examination of the interleukin 6 (IL-6) and procalcitonin levels, and neutrophil-lymphocyte ratio (NLR) might could help to diagnosis and predict the duration of therapy and prognosis of pneumonia cases. *Zingiber officinale* var rubrum could be used as an adjunct therapy in infectious diseases as it has anti-inflammatory activity. The aim of study was to assess the effect of Z. *officinale* on levels of IL-6 dan procalcitonin, NLR, and the length of hospitalization of patients with community-acquired pneumonia (CAP). An open-label clinical trial was conducted among CAP cases regardless of the etiology at Dr Moewardi Hospital and Universitas Sebelas Maret Hospital, Surakarta, Indonesia from July to September 2022. A total of 30 inpatient CAP cases were recruited and were randomly divided into two groups: (1) received *Z. officinale* capsule 300 mg daily for five days in addition to CAP standard therapy; and (2) received CAP standard therapy only, as control group. The data were compared using a paired Student t-test, Chi-squared test, Mann-Whitney test and Wilcoxon signed-rank test as appropriate. In *Z. officinale* group, the mean difference between post- and pre-treatment as follow: IL-6 level was 9.93 pg/mL, procalcitonin level -471.31 ng/mL, and NLR value -4.01. In control group, the difference was 18.94 pg/mL for IL-6, 339.39 ng/mL for procalcitonin, and 1.56 for NLR. The change of IL-6 was not statistically significant between treatment and control groups with p=0.917. The changes of procalcitonin level and NLR were significant between treatment and control group with p=0.024 and p=0.007, respectively, of which the treatment had better improvement. In addition, our data indicated that the length of stay was not statistically significant between the treatment and control groups (4.13 vs 4.47 days, p=0.361). In conclusion, *Z. officinale* could reduce serum inflammatory markers such as procalcitonin and NLR but it has little impact in reducing IL-16 level and the length of hospitalization of CAP patients.

Keywords: Pneumonia, ginger, *Zingiber*, procalcitonin, IL-6

Introduction

Pneumonia is an infection characterized by an acute inflammation of the lung parenchyma. About 75% of pneumonia patients required hospitalization and 10% of them were admitted to the intensive care unit due to complications such as sepsis, septic shock, and acute respiratory distress syndrome [1]. Pneumonia is classified based on epidemiology, etiology, and predilection

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or site of infection [2,3]. Base on of how pneumonia is acquired, it is categorized into community-acquired, hospital-acquired, healthcare-acquired, or aspiration pneumonia [2,3]. A study in Semarang, Indonesia, identified that the most common causal pathogens for community-acquired pneumonia (CAP) are influenza virus, followed by *Klebsiella pneumoniae* and *Streptococcus pneumoniae* [3].

Anti-inflammatory therapy can be an adjunct therapy in CAP cases because it could reduce the complications of the excessive systemic inflammatory responses without disturbing the local favorable inflammatory process and reducing the mortality rate [2]. Several herbals have useful anti-inflammatory activity [2]. One of the strategies to reduce the length of hospitalization is by providing additional therapy that suppresses the inflammatory process and therefore could accelerate the clinical improvement and shorten the length of hospitalization [4]. The use of anti-inflammatory therapy in some diseases has been carried out and has shown promising results [5,6].

Zingiber officinale var rubrum is often used in spices and traditional medicine and it contains oleoresin and essential oil that are higher than other types of ginger [7]. *Z. officinale* has anti-inflammatory, antiapoptotic, antiemetic, antitumor, antilipidemic, was well as has immunomodulator activities [8,9]. The use of *Z. officinale* is expected to help to suppress the inflammatory responses in pneumonia patients and this reduction could be measured using some markers such as interleukin 6 (IL-6), procalcitonin and the neutrophil-lymphocyte ratio (NLR) [10]. It is expected that the healing process could be faster and the length of antibiotics treatment could be shortened in order to reduce the antibiotic resistance [10]. To the best of our knowledge, there are no available studies assessing the effects of *Z. officinale* on the inflammation level of CAP patients. The aim of this study was to determine the effectiveness of *Z. officinale* in reducing the inflammatory markers (IL-6, procalcitonin and NLR) and the length of stay of patients with CAP thought a clinical trial. The results of this study are expected to be an alternative in providing additional therapy and being applied in clinical practice in treating CAP patients.

Methods

Study design and registration

An open-label clinical trial was conducted at Dr Moewardi Hospital and Universitas Sebelas Maret Hospital in Surakarta, Indonesia from July to September 2022. Inpatient CAP cases were recruited and randomly divided into two groups: treatment and the control groups. The treatment group received *Z. officinale* capsule 300 mg daily for five days as well as CAP standard therapy while control group received the CAP standard therapy only. The progress of the patients was followed until the end of hospitalization (recovered and discharged). The blood was collected from each patient of both groups at the first and after five days of treatment and the levels of IL-6 and procalcitonin, as well as NLR were measured. In addition, the length of stay of patients was also reordered as an outcome.

The clinical trial was registered at Thai Clinical Trials Registry (TCTR 20230414002 - https://www.thaiclinicaltrials.org/show/TCTR20230414002).

Sample size and randomization

To determine the minimum number of samples, error rate parameter of 0.05 and power of 90% were used. The minimal sample size required in this study was test 11 patients for each arm. However, considering the dropout possibility, additional 20% was added and therefore 15 CAP patients were recruited for each group. The CAP patients were randomly divided into treatment or control according to the order of entering the hospital.

Patients

The CAP patients receiving treatment at Dr. Moewardi and Universitas Sebelas Maret Hospitals during July to September 2022 were recruited and divided into two groups (treatment and control). The inclusion criteria of the patients were: (1) met the diagnostic criteria of CAP based on Indonesian Society of Respirology guideline; (2) confirmed by pneumonia symptoms such as cough, change/purulence of sputum color, fever, or breathlessness; and (3) had pneumonia sign

by chest X-ray (infiltrate of pneumonia). All patient with severe CAP, having cardiopulmonary failure, physical disfunction who could not complete the study, and patients with mental problem or communication difficulty were excluded.

For each patient, the Pneumonia Severity Index (PSI) was assessed [11]. PSI consists of 20 parameters to stratify the risk and prognosis of the patient including demographic characteristics (gender or nursing home resident), co-morbid (neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease and renal disease), examination findings (the presence of altered mental status, respiratory rate, systolic blood pressure, temperature and pulse) and laboratory findings (pH, blood urea nitrogen (BUN), serum sodium, serum glucose, hematocrit, and PaO_2) as well as the presence of pleura effusion. The PSI scores were calculated using method explained elsewhere [11]. The matching of PSI scores was conducted between patients within treatment and control groups before included in the study.

Intervention

In treatment arm, the patients received oral *Z. officinale* capsule 300 mg daily for five days as well as the CAP standard therapy. The *Z. officinale* capsules were purchased from PT Industri Jamu dan Farmasi Sido Muncul Tbk (The Indonesian Food and Drug Authority, Registration number (POM TR): 202352561). The patients within control group received no placebo. Both treatment and control groups received standard therapy of CAP including antibiotic such as IV levofloxacin 750 mg once daily or IV ceftriaxone 2 gram once daily), mucolytic such as oral N-acetylcysteine 200 mg three times daily or oral ambroxol 30 mg three times daily and antipyretic paracetamol 500 mg three times daily.

End points

The end points were the inflammation markers (IL-6 level, procalcitonin level and NLR) as well as the length of stay. The levels of IL-6 and procalcitonin as well as NLR were measured at the first day of admission (before the treatment) and after five days of treatment. The quantitative assay Interleukin-6 Human ELISA kit (DE2132) was used to measure the level of IL-6 following the manufacturers' protocol (Demeditec Diagnostics GmbH, Kiel, Germany). The detection range of the kit is 1.56-100 pg/mL. The absorbance was measured using wavelength of 450 nM and 640 nM. The level of prolactin was measured using quantitative Procalcitonin Human ELISA kit following the manufacturers' instruction (E-EL-H1492, Elabscience Biotechnology Co., Ltd, Wuhan, Hubei, China). The absorbance was measured using wavelength of 450 nM.

For all patients, the physical examination and clinical improvement were monitored daily and the length of stay was calculated as the number of days required between the day of admission and the discharged day.

Statistical analysis

The categorical data was presented using frequency distribution (%) while numerical data using mean ± standard deviation (SD). To compare the categorical data between unpaired groups, the Chi-squared test was used. Independent Student t-test or Mann-Whitney test were used to compare the numerical data between unpaired groups as appropriate with the data. The Wilcoxon signed-rank test was used to compare the numerical data between paired groups. Data analyses were conducted using SPSS 21 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics

A total of 30 CAP completed the follow-up of which the basic characteristics of the patients are presented in **Table 1**. Our data indicated that the age, gender, PSI score, and smoking history of the patients had no significant difference in both groups. All the CAP patients included in both groups had mild severity with the PSI mean scores were 60.93±16.75 and 60.93±9.97 for treatment and control group, respectively, indicating II-III risk class.

Table 2. Baseline characteristics of community-acquired pneumonia patients included in the study (n=30)

Patient characteristics	Group		*p*-value
	Treatment (n=15) Mean±SD	Control (n=15) Mean±SD	
Sex			0.464 [a]
Female	6 (40.0%)	8 (53.3%)	
Male	9 (60.0%)	7 (46.7%)	
Age (year)	58.27±15.17	58.60±9.77	0.943 [b]
Pneumonia Severity Index score	60.93±16.75	60.93±9.97	1.000 [b]
Smoke			0.715 [a]
No	7 (46.7%)	8 (53.3%)	
Yes	8 (53.3%)	7 (46.7%)	
Interleukin 6 (pg/mL)	60.46±74.87	78.40±121.49	0.885 [c]
Procalcitonin (ng/mL)	789.92±951.11	503.35±718.87	0.694 [c]
Neutrophil-lymphocyte ratio	9.19±5.26	6.16± 3.16	0.067 [b]
Respiratory rate (/min)	26.13±2.56	28.00±3.68	0.134 [c]
Systolic blood pressure (mmHg)	108.67±17.25	116.00±14.24	0.125 [c]
Temperature (°C)	36.55±0.30	36.67±0.31	0.239 [b]
pH	7.42±0.03	7.40±0.03	0.132 [c]
Blood urea nitrogen (mmol/L)	11.97±3.52	13.16±3.34	0.256 [c]
Serum sodium (mEq/L)	130.20±4.04	130.14±6.61	0.978 [b]
Serum glucose (mmol/L)	149.87±35.30	131.00±32.94	0.110 [c]
Hematocrit (%)	36.13±6.57	33.87±7.95	0.402 [b]
PaO2 (mmHg)	121.27±24.31	126.00±37.23	0.800 [c]

SD: standard deviation
[a] Analyzed using Chi-squared test
[b] Analyzed using independent Student t-test
[c] Analyzed using Mann-Whitney test

Effect of *Z. officinale* on IL-6, procalcitonin and NLR

During the course of treatment, the level of IL-6 increased 9.93 pg/mL (60.46 pg/mL before the treatment vs 70.39 pg/mL for post-treatment) in the treatment group (**Table 2**). In control group, the IL-6 level increased 18.94 pg/mL compared to baseline data (78.40 vs 97.34 pg/mL). The change of IL-6 was not statistically significant between treatment and control groups with *p*=0.917 (**Table 2**), suggesting *Z. officinale* was not effective in reducing IL-6 in CAP patients.

Table 2. Comparison of IL-6, procalcitonin and NLR between treatment and control groups before and after the treatment

Variables	Phase	Group		*p*-value
		Treatment Mean±SD	Control Mean±SD	
IL-6 (pg/mL)	Pre-treatment	60.46±74.87	78.40±121.49	0.885 [a]
	Post-treatment	70.39±161.09	97.34±181.73	0.468 [a]
	p-value	0.523 [b]	0.609 [b]	
	Delta changes (post-pre)	9.93±172.83	18.94±145.00	0.917 [a]
Procalcitonin (ng/mL)	Pre-treatment	789.92±951.11	503.35±718.87	0.694 [a]
	Post-treatment	318.60±517.83	842.74±953.31	0.065 [a]
	p-value	0.005 [b*]	0.496 [b]	
	Delta changes (post-pre)	-471.31±744.59	339.39±812.16	0.024 [a*]
Neutrophil-lymphocyte ratio	Pre-treatment	9.19± 5.26	6.16± 3.16	0.067 [a]
	Post-treatment	5.17± 3.53	7.73± 7.05	0.221 [a]
	p-value	0.028 [c*]	0.307 [b]	
	Delta changes (post-pre)	-4.01± 6.32	1.56± 6.09	0.007 [b*]

[a] Analyzed using Mann-Whitney test
[b] Analyzed using Wilcoxon signed-rank test
[c] Analyzed using independent Student t-test
* Statistically significant at *p*=0.05

The mean level of pre-treatment procalcitonin was 503.35 ng/mL and the post-treatment was 842.74 ng/mL among patients within the control group, indicating an increase. In contrast, patients within the treatment group had significant reduction of procalcitonin level with an average 471.31 ng/mL between pre-treatment (789.92 ng/mL) and post-treatment (318.60 ng/mL) (**Table 2**). Statistical analysis suggested that the change of procalcitonin levels was significant between treatment and control group (p=0.024) (**Table 2**). This suggests that *Z. officinale* was effective in reducing procalcitonin level in CAP patients.

In the control group, the mean pre-treatment and post-treatment NLR was 6.16 and 7.73, respectively suggesting a sightly increase. In treatment group, however, the mean post-treatment NLR reduced significantly compared to pre-treatment (9.19 vs 5.17; with mean reduction of 4.01) (**Table 2**). Our data indicated that the change of NLR was significantly different between treatment and control groups with p=0.007 (**Table 2**).

Effect of *Z. officinale* on the length of stay

The mean length of stay of CAP patients within treatment group was 4.13±0.92 days while in the control group was 4.47±0.92 days. Although, the length of hospitalization in the treatment group slightly shorter, length of stay was not statistically significant between the treatment and control groups (p=0.361).

Discussion

We did a clinical trial to assess the effectiveness of *Z. officinale* in reduction of inflammation processes and length of stay of patients with CAP. *Z. officinale* has been widely studied and had antibacterial activity against Gram-positive and Gram-negative bacteria [8,12]. It contains oleoresin and essential oil, shogaol and 6-gingerol where these substances could inhibit tumor necrosis factor alpha (TNF-α) directly or inhibit the increase of nuclear factor kappa B (NF-κB) which is associated with the formation of proinflammatory cytokines [10-13]. A study in mice models found that the administration of *Z. officinale* increased the anti-inflammatory cytokines including IL-10 and reduced the proinflammatory cytokines such as TNF-α, IL-6, and IL-1β [14].

In this clinical trial, the reduction of inflammation processes was assessed using three indicators: IL-6, procalcitonin and NLR. Procalcitonin, an amino acid peptide, has good prognostic value and accuracy for diagnosing pneumonia [4]. The liver produces procalcitonin in an acute phase by C cells of thyroid and K cells of lungs as reactant [4,15]. Bacterial-specific proinflammatory cytokines such as IL-1β, TNF-, and IL-6 as well as endotoxins stimulate procalcitonin release from tissue parenchyma within two hours of exposure to infection and then reach a peak after 12–48 hours and gradually decrease in 48–72 hours [15]. Procalcitonin is also an important marker of inflammation and infection especially in severe bacterial infections, sepsis, septic shock, and multiorgan dysfunction syndrome (MODS) [4,15]. NLR can be used as an indicator of the systemic inflammatory response due to pneumonia infection [16,17]. IL-6 has a role as an activator of the immune system, inflammation, and metabolic control [18]. It is the most studied cytokine in sepsis and is most commonly found to be elevated in patients with pneumonia [18] and has been used as a biomarker of proinflammatory cytokine activation [19].

Our data suggested that *Z. officinale* was not effective in reducing serum IL-6. There are some plausible explanations and one of them is IL-6 has a long plasma half-life and many lung parenchyma cells such as alveolar macrophages, type II pneumocytes, T lymphocytes, and lung fibroblasts produce IL-6 [18]. Among pneumonia patients with acute respiratory distress syndrome (ARDS), IL-6 level decreased in on the 7th day [18]. A study with coronavirus disease 2019 (COVID-19) pneumonia showed a decrease in IL-6 level occurred after day 8 of therapy [19]. In our study, IL-6 was measured after day 5 of *Z. officinale* administration.

Our study suggested that *Z. officinale* treatment was effective in reducing serum procalcitonin. Procalcitonin is a specific biomarker of bacterial infection [15] and it can be used as a diagnosis, guideline for giving antibiotics, as well as to assess the response to therapy in pneumonia patients [20]. However, could not predict the etiology and is less sensitive to viral infections [21]. Decreased procalcitonin level is good marker of clinical improvement in

pneumonia and can be used to guide antibiotic discontinuation [21]. Procalcitonin increases 6–12 hours after infection and it will drop once the infection is under control [21].

Our study also found that *Z. officinale* capsules were effectively to reduce NLR. It has been well known that NLR can be used as an indicator of the systemic inflammatory responses [22]. NLR is easy to be measured and is an inexpensive parameter because it can be calculated through the results of a complete blood count. A study in 2017 found that NLR increased among inpatient compared to the outpatient groups; it was a good marker of inflammation; and it could predict 30-day mortality in CAP patients [23]. The cut-off value for the NLR in predicting patients with CAP was 2.54 with a sensitivity of 83% and a specification of 44% [23]. NLR could predict the mortality better than C-reactive protein level, white blood count, neutrophil count, and lymphocyte count [23]. Our data, however, indicated that *Z. officinale* did not reduce the length of stay of CAP patients. Nevertheless, a study in 2020 indicated a lower hospitalization rate among *Z. officinale* users (28.0%) than non-users (38.0%) in COVID-19 pneumonia [24].

There are some limitations of this study that need to be discussed. This is an open-label clinical trial with relatively small sample size and therefore further clinical trials with blinding and larger sample size need to be conducted. In this study, the controls did not receive placebo that have similar with *Z. officinale*. Although the use of placebo is debatable [25], it needs to be prepared in the further clinical trial. Finally, this clinical trial had only one dose of *Z. officinale* (300 mg daily) and having more than one doses will be critical in the further trial.

Conclusion

Our data suggest that the *Z. officinale* 300 mg daily is effective in reducing some serum markers of inflammation process such as procalcitonin and NLR in CAP patients. Therefore, the administration of *Z. officinale* could be an adjuvant therapy option in pneumonia cases. A larger clinical trial with blinding and larger sample size however is still important to validate this preliminary clinal study.

Ethics approval

This clinical trial was approval by Medical Ethics Committee of Dr Moewardi Hospital (420/IV/HREC/2022) and Universitas Sebelas Maret Hospital (2282/UN27.46/TA.04.19/2022). All patients voluntarily signed the informed consent.

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Conflict of interest

The authors declare that they have no competing interests.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

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