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Influence of zinc supplementation in eosinophil nasal mucous count and quality of life in moderate to severe persistent allergic rhinitis patient in ENT clinic Dr. Kariadi hospital Semarang in November 2016 until January 2017

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ABSTRACT

Background: Allergic rhinitis is an inflammation in nasal mucous caused by allergen exposure. Eosinophil has a role the allergic reaction. Examination of eosinophil nasal mucus is a cytologic investigation to diagnose AR. Zink is a micro, and essential nutrient with anti-inflammatory effect suggest to reduce eosinophil nasal mucous and increase the quality of life.

Objectives: To determine the effect of zinc supplementation on a mount of eosinophil nasal mucous and quality of life in moderate to severe persistent allergic rhinitis patient.

Methods: A single-blinded intervention study pre-test and post-test design.The treatment of zinc 40 mg/24 hour in the moderate to severe persistent allergic rhinitis patient with cetirizine (experimental group) is compare with treatment of cetirizine only (control group). The examination of the zinc serum count of nasal mucous eosinophil and the quality of life in the first and second week after the treatment was compare beetwen the two groups.

Result: A total of 34 subjects included in the study. There was a significant decrease in the eosinophil count of nasal mucus in experimental group (p=0.002) and the control group (p=0.001). However the eosinophil count f nasal mucus beetween these groups after intervention showed no significant diference (p=0.375). In contras, the quality of life score between these grups after the intervention is statistically significant (p=0.046).

Conclusion: The Zinc supplementation decreases the eosinophil count of nasal mucous before the intervention. However, there is no significant difference between the two groups after the intervention. The Zinc supplementation showed an increase in the quality of life in moderate to severe persistent allergic rhinitis patient.

Keyword : moderate to severe persistent allergic rhinitis, zinc, eosinophil of nasal mucous, quality of life.

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INTRODUCTION

Allergic rhinitis is an inflammation in nasal mucous caused by allergen exposure, mediated by Ig E, and it is a tipe I hypersensitivity reaction. The allergic characterized by the by the local accumulation of inflammatory cells such as T-Lymphosit, mast cell, eosinophil, basophil and neutrophil in the blood and the tissue.[1,2] The prevalence of allergic rhinitis is increases in developing countries. It is expected that ocurrence of allergic rhinitis is 10-30% in adults and more than 40% in children. Research on junior high school students 13-14 years old in Semarang (2001-2002) shows prevalence of AR is 18.6% which are consisted with the moderate persistent (51%), mild persistent (23%) and mild intermittent AR (22%). The characteristic data of AR patient in the ENT clinic of Dr. Kariadi Semarang in 2009 mostly was diagnosed with a persistent AR (64.1%).[4]

The eosinophils play an essential role in the allergic reactions by releasing primary protein mediators, arachidonic acid metabolites and cytokines that contribute to the mucosal inflammation and the emergence of hypereactive or hyperresponsive symptoms of the nose. The examination of the nasal mucosal eosinophils is one of the cytological examinations that can be used to diagnose and evaluate therapy of AR.[5,6] The treatment is targeted to overcome the symptoms that occur during the fast-phase allergic reactions (RAFCs) as well as the slow-phase of the allergic reactions (RAFL).[7] The treatment of persistent severe AR patients use the intranasal corticosteroids and antihistamines for 2 to 4 weeks, but not all AR patients can get intranasal corticosteroids because they are not necessarily available or not all AR patients have health insurance.

Zinc is an essential micronutrient for growth, development, maintenance, immune system, and tissue repair. The inc deficiency can cause an

imbalance between the Th1 and the Th2 function, the increase in the serum zinc level can significantly decrease the Th 0 cell activity which leads to the change in the ratio of Th1/Th2 that will worsen the allergic inflammation.[3,8] The anti-inflammatory mechanisms of zinc were resulted from; (1) The inhibition of the monopolysaccharide and the interleukin-1β that induce NO formation; (2) the inhibition of the activation of Nuclear Factor-Kappa Beta (NF-κβ), which is involved in pro-inflammatory gene expression; (3) The innhibition of the preform mediators release from the mast cells and basophils (e.g. histamine) and eosinophils (e.g. protein cationic eosinophils); (4) the modulation to the immune system through the NFκβ pathway, as transcription factors that control several immune response genes and decrease the inflammatory response. Zink is expected to be an alternative to corticosteroid for anti-inflammatory therapy.[3,9] The purpose of this study is to prove that the zinc supplementation can decrease the number of nasal mucosal eosinophils and improved the quality of life in patients with a severe persistent allergic rhinitis.

METHODS

This research is an intervention with pre-test and post-test randomized controlled trial design. The subjects were the allergic rhinitis patients who went to the Allergy-Immunology of ENT clinic in Kariadi general hospital from November 2016 to January 2017. This research was approved by the medical research ethics committee of the Faculty of Medicine Diponegoro University - Dr. Kariadi Semarang. (Approval No.1.015/EC/FK-RSDK/XI/2016). The inclusion criteria were male or female patients aged 15-55 years old, meeting the diagnosis of moderate-severe persistent severe allergic rhinitis (WHO 2008 ARIA Criteria), a positive prick test results of 3 or more of one or more aeroallergens, oral or topical corticosteroid-free drugs, oral or topical decongestants and antihistamines for 1 week, and willing to be included in the study. The patients with diseases that may affect treatment outcomes such as: rhinosinusitis, nasal polyps, nasal tumors, pregnant women and patients undergoing specific immunotherapy were excluded from the study. A total of the 34 sujects was divided into two groups of control and treatment group consisted of 17 sujects in each group. The sampling was done with the consecutive sampling. The treatment group received the zinc 40 mg/24 hours and cetirizine ten mg/24 hours while control group received cetirizine 10mg/24 hours. The drug was randomized with simple random and single blinding methd. The nasal mucosal eosinophils, the zinc levels in blood and the quality of life score by using quesionare with six domain consist of; sleep, nasal symptom, allergic symptom, practical problem, activity and emotion. Threre are 26 question included. The score classified into; 0 for no lamentation, 1 for mild lamentation no irritate, 2 for moderate lamentation, irritate but no activity distraction, 3 for moderate to severe lamentation and activity distraction, 4 for severe lamentation with activity and sleep disturbance. Emotion score classified into; 0 for never 1 for very rarely, 2 for rarely 3 for often, 4 for very often or always. were measured before treatment in each group. The measurement was done in the second week after therapy which is then compared between the two groups. The grading of the eosinophils was done using the Naclerio criteria, based on the number of eosinophils per ten fields of view.[6] It classified into; negative (-) if no eosinophils are found per ten fields. positive (+1) for 1-5 eosinophils per ten fields of view; positive (+2) for 6-15 eosinophils per ten fields of view; positive (+3) for 16-20 eosinophils per ten fields of view; and positive (+4) for > 20 eosinophils per ten field of view. The examination of eosinophil smear was done by the laboratory of microbiology department of the medical faculty of Diponegoro University (UNDIP), while plasma zinc concentration was done by laboratory analyst GAKI of UNDIP medical faculty. The comparison test in one group was analized using a paired t-test or Wilcoxon test. The comparative test analysis between the two groups was analyzed using unpaired t test or Mann Whitney test.

RESULTS

The study was conducted from December 2016 until March 2017. A total of 41 patients were recruited fr the study. From theses patients, two patients refused to follow the study, five people suffered from a mild intermittent allergic rhinitis. Hence a total of 34 patients who met the inclusion and exclusion criteria were taken as the subjects of the study, which is divided into two groups of control and treatment groups consist of 17 subjects in each group. The age range of the patients was between 20 and 46 years old. The mean age in the control and treatment groups was similar for 25 and 23 years old, respectively. The treatment and control groups consisted of women for 82.4% and 70.6% respectively. There was no significant difference in sex between the treatment and control groups. The majority of the patients (941%) in both grups went to college. The characteristics of th groups can be seen in Table 1. There was a decrease in the allergic symptm and

Table 1 **The characteristics of the allergy symptoms, duration of illness, incidence and frequency of pain in the control and treatment groups**

Variable N=34	Group		p
	Control n=17	Treatment n=17	
Clogged nose n(%)			
No symtoms	0 (0)	2 (11,8)	0,355¥
Mild	3 (17,6)	5 (29,4)	
Moderate	9 (52,9)	7 (41,2)	
Severe	5 (29,4)	3 (17,6)	
Runny nose n(%)			
No symtoms	1 (5,9)	2 (11,8)	0,096¥
Mild	10 (58,8)	3 (17,6)	
Moderate	5 (29,4)	11 (64,7)	
Severe	1 (5,9)	1 (5,9)	
Sneezing n(%)			
No symtoms	2 (11,8)	0 (0)	0,347¥
Mild	4 (23,5)	5 (29,4)	
Modearate	7 (41,2)	10 (58,8)	
Severe	4 (23,5)	2 (11,8)	
Itchy nose n(%)			
No symstoms	1 (5,9)	1 (5,9)	0,565¥
Mild	8 (47,1)	5 (29,4)	
Moderate	5 (29,4)	9 (52,9)	
Severe	3 (17,6)	2 (11,8)	
Duration of Ilness (mean±std deviation)	9,37 ± 6,45	9,21 ± 6,92	0,944‡
Time of attack n(n%)			
Afternoon	1 (5,9)	3 (17,6)	0,601¥
Night	13 (76,5)	12 (70,6)	1,000¥
Morning	16 (94,1)	17 (100)	1,000¥
Frequency of attack,time (range)	5 (2 – 7)	4 (4 – 7)	0,712¶

Note : ‡ Independent t; ¶ Mann Whitney; ¥ Chi Square test

Table 2 **Differences in zinc levels before and after treatment**

Zinc (µ/dl)	Group		p
	Control n=17	Treatment n=17	
Pre test	63,14 ± 18,37	63,91 ± 20,28	0,908 ‡
Post test	79,37±40,26	73,38±25,47	0,890 ¶
p	0,029 *£	0.039 *£	

Note :‡ Independent t; ¶ Mann Whitney, * Significant, £ Wilcoxon

the quality of life score in the first and second week compared to the start of the study Figure 1).

The mean blood zinc level before the intervention in the control group was and the treatment group was 63.14 µ / dL and 63.91 µ / dL respectively. There was no significant difference in the blood zinc level between both groups before the intervention (p-value = 0,908). The highest number of the nasal mucosal eosinophils in the control and treatment group were +2 (35.2%) and +4 (41.1%), respectively.

The nasal mucosal eosinophils counts of the control group in pre and post-test are negative (12) to +1 (5)post-test compare to +2 (6), +3(3) +4(4), respectively(p = 0.001).While, the nasal mucosal eosinophils count in the treatment group pre- and post-test are negative (14) and +1 (3) and +2 (4), +3(2) +4(7), respectively (p = 0.002)

The number of nasal mucosal eosinophils after treatment in both groups is not statistically significant (p=0.375) for negative (12) to +1 (5) in the control group and negative (14) to +1 (3) in the treatment group.

The meanof the quality of life score in the second week is higher in the control than the treatment group for 12 (2-55) and 20 (0-51) with a p value of 0.046. The mean of the quality of life score in the control group in the starting week is higher than the second week for 44,47 ± 16,25 and 22,71 ± 16,98 (p<0.05). While the mean of the quality of life score in the treatment group in the starting week is higher than the second week for 29 (14-68) and 12 (2 – 55)(p<0.05).

DISCUSSION

Characteristics of the subjects

The study included 34 patients between the age of 20 and 46 years old with a severe persistent allergic rhinitis. The mean age in contrl and treatment group were 25 and 23 years old respectively.This finding was similar to the previous research showing that the allergic rhinitis is more common in young adulthood and decline at the age above 50 years. The study in Bandung reported that the allergic rhinitis was found in the aged 20-40 years and 20-29 years for 65.2% and 30% respectively.[18,19] The research in Europe (2007) found that 80% of cases occur at the age of 28 years old. This productive group is more likely to be exposed to an allergen which causes the allergic rhinitis. More over, the subjects of this study mostly were consisted of women (76.5%) than men (23.5%). A similar composition of the subjects was found in the studies conducted in Manado (2012) and Bandung (2010).[19,20] It is possible that the reason women had allergic rhinitis more often than men was because they are more exposed to dust during the household chores.

The most commonly found symptoms in both groups were sneezing and nasal congestion. This

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Table 3 Number of nasal mucosal eosinophils after treatment in both groups

Group	Eosinophil Count					p
	Negative	+1	+2	+3	+4	
Control	12	5	–	–	–	0,375¶
Treatment	14	3	–	–	–	

Note : * Significant ; ¶ Mann Whitney

Table 4 The average Quality of Life Score for each group

Variables	week		p
	Start	II	
Control	44,47 ± 16,25	22,71 ± 16,98	0,000*§
Treatment	29 (14 – 68)	12 (2 – 55)	0,000*£

Note : * Significant; § Paired t-test; £ Wilcoxon

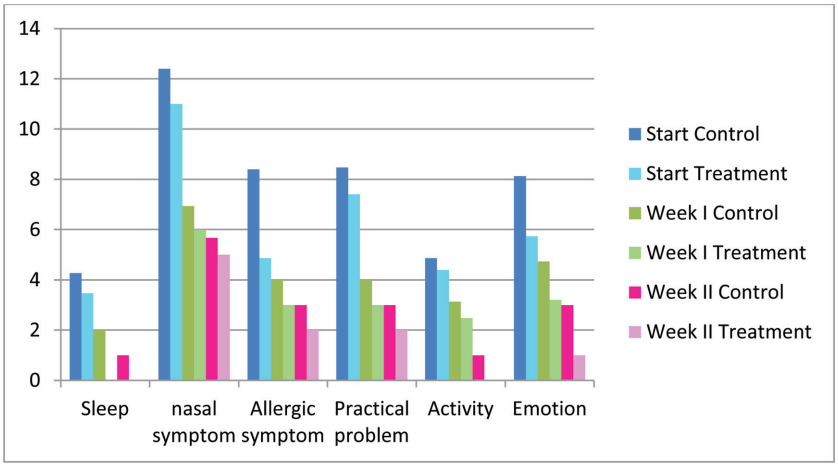

Figure 1 The Quality of Life of the control and treatment groups

result was also found in several studies across countries which is varied between 64-84%. Sneezing is a rapid phase symptom in AR caused by the histamine bonding of the neural receptors type C nocsiceptive in NV in the nasal mucosa which cause the itchy nose and stimulated to sneeze. The symptoms of a blocked air way occure in a slow-phase reaction caused by the persistent allergen exposure and infiltration of inflammatory cells (eosinophils and T cells) in the tissues, venous dilation of the nasal mucosa, increased vascular permeability, mucosal edema and excessive secretion.[2] The mean age of patients suffered from these symptoms in the control group and treatment group were 9.37 years and 9.21 years respectively. Research in Semarang (2011) found that the mean age of AR patients is 6.47 year with a range of 1 year until 20 years old. AR is a chronic disease. These patients seek treatment when it is starting to interrupt their of daily activities. These symptoms are most likely to occur in the morning for both of the groups. Previous research found that 70% of AR patients experience an increased frequency of sneezing, nasal congestion and watery snot in the morning.[21] Moreover, several studies showed an increase in allergic inflammatory mediators highest in the morning that is causing more prominent symptoms.[21] Further more, this study found a consistent finding with the literature of persistent AR regarding the frequency of the attack in the AR patient for 4 to 5 days a week.

The blood zinc levels in the control and treatment group were 63.14 µ / dl and 63.91 µ / dl respectively. The finding in this study consists the normal serum zinc level is 50-150 µ / dl in the literature.[46] The number of nasal secretions of eosinophils of +2 in this control group and +4 in the treatment group was 35.2% and 41.1% respectively. This is consistent with the literature that eosinophils plays a role in allergic processes and accumulates in the nasal mucosa as a normal target organ which cannot e found in a healty personal.[5,14] The number of different nasal secretions of eosinophils can be caused by the small number of allergens present around the patient.[14]

Previous research, the persistence of RA symptoms has a significant relationship with allergen mite culture and cockroach type 41% each. Mite develops at temperatures above 20°C and moisture is relatively 80%.[2] This is in accordance with the average temperature in Indonesia around 23-30°C with high humidity so that mite culture can develop well. The most common side effects of zinc in this study were nausea and taste changes in the mouth. No severe side effects such as vomiting or diarrhea cause dehydration. This result is in accordance with the results of meta-analysis research in Canada (2012) obtained 33.7% of samples in the zinc group felt the change in tasting and 16.7% samples felt nausea.[10]

Differences of zinc levels before and after treatment

The blood zinc level was significantly increased in both control and treatment groups after treatment ($p<0.05$). How ever the blood zinc level after treatment compare between the control and the treatment groups was no statisticaly significant ($p>0.05$). This difference in the zinc level may be affected by various factors. The zinc absorption depend on the bioavaibility of zinc. The zinc from the animal products is more readily absorbd than vegetale products because of the phytate and plant fibre contents that bind zinc. Other nutrients such as iron, phosphate, lead, cadmium, calcium, and copper can inhiit the zinc absorption. Zinc is mostly absorbed in the duodenum and the proximal part f the small intestine (20-30%), which then across

the serous surface and actively secreted int the portal circulation where zinc is bound to albumin. Zinc in blood plasma is bound and transported by alumin (60%), and transferrin (10%).[15] Moreover, An acute or inflamatory infections will decrease the zinc levels due to the redistribution of zinc from plasma to liver mediated by endogenous leukocyte mediators. The low molekular weight ligand such as amino acids and other organic acids can increase the solubility and facilitate absorption. The cysteine and methionine increased the zinc absorbtion by forming the stable complexes with zinc.[22,23] Furthermore, Rahmawati N (2016) suggested that the zinc supplementation my increase the serum level. The study showed an increase in the serum levels of 36.2µg/dl with zinc supplementation of 20 mg/8 hours for seven days in acute ischemic stroke patients.[24] The meta-analysis study conducted in Europe supported this finding. It shows that zinc intake of 14 mg/day for six month had increased the serum zinc by 9%.[25] There for the difference in the blood zinc level in AR may not solely caused by the inflammation process but can be resulted frm the intake and can be resulted from the intake and absorption.

Differences in the number of nasal mucosal eosinophils

The number of nasal mucosal eosinophils and the eosinophil count in the control gand the treatment group before and after treatment was statistically significant with the p-value <0.05 A previous study revealed that allergic rhinitis is characterized by the recruitment of eosinophils to the nasal mucosa. The process of migrating eosinophils from blood vessels to the nasal mucosa through several stages of progenitor cell differentiation, proliferation, eosinophil and endothelial interactions that include rolling, adhesion, and eosinophil cell migration, and eosinophil chemotactics that bring eosinophils directly to the specific locations, as well as the activation and destruction of the eosinophils.[12]

The eosinophils migration from the peripheral blood vessels to the nasal mucosa was determined by the cytokines (IL3, IL5, and GM-CSF), chemoattractante (leukotriene B4, platelet activating factor) cytokines in the nasal mucosa and CC-chemokine (eotaxin, eotaxin-2, RANTES).[13] The eosinophils at the allergic sites will result in mucosal changes due to the release of various mediators contained in the eosinophil cell granules. The mediators include *major basic protein* (MBP), *eosinophil cationic protein* (ECP), *eosinophil derived neurotoxin* (EDN), *eosinophil peroksidase* (EPO), and leukotrienes (LTs). The MBP inhibits the ciliary activity in mucosal cells, damages respiratory epithelial, cytotoxic and may increase microvascular permeability. The ECP and EPO in addition to being cytotoxic, causinig histamine release that may increase the microvascular permeability and damage the epithelium. The leukotrienes result in the nasal sinusoid congestion that causes conjunctive edema, which lead to the worsenings of nasal obstruction symptom.[15] The zinc is a useful in patients with allergic rhinitis because it has various functions such as anti-oxidants, maintaining wholeness and ciliary function in respiratory epithelial epithelia, for DNA synthesis and cell growth, to assist the re-epithelialization, and to have anti-inflammatory effects. The binding of the zinc ions to the ICAM and VICAM prevents the binding of eosinophils in the nasal mucosa which lead to the suppression of the inflammatory response. The anti-inflammatory affect of zinc inhibits the activation of NFκβ which causes the activation of cytokines and adhesion molecules. Zinc inhibits the release of inflammatory mediators from eosinophils such as ECP which is an eosinophil granule, with MBP, EDP, and EPO leading to hyperreactivity or hyperresponsiveness of the nose.[16] Zinc supplementation is expected to decrease the nasal mucosal eosinophils. The study showed a significant reduction in the nasal mucosal eosinophil count (p-values <0.05) in the control and treatment groups before and after treatment. While, the nasal mucosal eosinophil count after treatment between the control and treatment groups were not statistically different (p> 0.05) which may be caused by various factors such as, the number of different nasal secretions of eosinophils, the small number of allergens present around the patient absorption and the albumin and transferrin-mediated distribution of zinc in the body.

Quality of Life Score

The quality of life measured the sleep domain nasal symptom allergy symptom, practical problems, activities, and emotions.The quality of life score, decreases at the week II compared with the week I and the beginning of the study. There was a significant difference between the control and treatment groups at week II. The administration of allergy medicines leads to the improvement of the allergy symptoms which indirectly increase the quality of life. Zink protects the respiratory tract epithelium from the exposure to allergens, inhalant pollutants, and viruses in the environment that can cause inflammatory reactions. The combination of anti histamines and zinc can inhibit the activation of the inflammatory mediator. The alleviation of the symptom improves the quality of life of the AR patients. This result is consistent with the result of the study conducted in the United States (2014) on

the effectiveness of cetirizine 10 mg for four weeks on the quality of life of Rine Perineal patients.[25] Moreover Setyorini D (2014) found that there was an improvement of symptoms and quality of life score at the week to week II after the 40 mg Zinc supplementation for 14 days.[11]

In conclusion, the Zinc supplementation decreased the number of nasal mucosal eosinophils with persistently severe AR. The number of nasal mucosal eosinophils of persistent severe AR patient treated with a zinc supplementation was not significantly different than those without the zinc supplementation. However, the Zinc supplementation has shown to reduce the Quality of Life Score of the persistent severe AR patients. The severe persistent AR with zinc supplementation was significantly different than without zinc supplementation. Therefore, further research on the effect of zinc supplementation on patients with severe persistent AR by using other inflammatory mediator parameters such as IL 3 and IL 5 is needed to explore other inflammatory mediators.

CONFLICT OF INTEREST

Author declares there is no conflict of interest regarding all aspect of the study.

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