ORIGINAL ARTICLE

Comparison of Neutrophil Eosinophil Ratio (NER) in Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) and Chronic Rhinosinusitis without Nasal Polyps (CRSsNP)

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Abstract

Introduction: Chronic rhinosinusitis is one of the most common world health problems and affects the quality of life. Recent research suggests differences in immunological mechanisms in immunological endotypes between chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). Identifying the neutrophil eosinophil ratio (NER) in CRSwNP and CRSsNP is important to determine the type of inflammation so that pathophysiological differences can be known and appropriate therapy can be given.

Materials and methods: Cross-sectional study involved 24 subjects. The subjects are divided into two groups based on the phenotype, 12 CRSwNP and 12 CRSsNP. This research uses maxillary sinus mucosa to identify the levels of neutrophils and eosinophils in the maxillary sinus mucosa using flow cytometry. NER in CRSwNP and CRSsNP was analyzed statistically using student *t*-test.

Results: The mean of neutrophils in CRSwNP: 5.31 ± 0.24% (N:1.1–1.7%) and CRSsNP: 4.29 ± 2.42% (N:1.1–1.7%). The mean of eosinophils in CRSwNP: 4.76 ± 2.55% (N: 0.3–0.7%) and CRSsNP 3.60 ± 2.88% (N: 0.3–0.7%). The average NER in CRSwNP was 1.33 ± 0.71 (N:2.8), and CRSsNP was 2.58 ± 3.07 (N:2.8). The results were not significantly different in the two groups ($p = 0.196$). In CRSwNP and CRSsNP, as many as 83.33% of the subjects had an eosinophilic type of inflammation.

Conclusion: There were no significant differences in NER and type of inflammation between chronic rhinosinusitis with polyps and without polyps.

Keywords: Chronic rhinosinusitis with nasal polyps, Chronic rhinosinusitis without nasal polyps, Neutrophil eosinophil ratio.

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Introduction

Chronic rhinosinusitis is one of the most common inflammatory diseases worldwide.[1,2] Chronic rhinosinusitis is an inflammation involving the paranasal sinuses and nose that lasts longer than 12 weeks. At least two symptoms must be present, one of which is nasal congestion or nasal discharge and the other, such as facial pain or reduced or loss of the ability to smell. In addition, an endoscopic examination may reveal nasal polyps and mucopurulent secretions from the middle meatus, edema, and mucosal obstruction in the middle meatus. A CT scan revealed changes in the osteomeatal complex and sinuses.[3] Chronic rhinosinusitis is a multifactorial disease with different etiology and pathophysiology resulting from a dysfunctional interaction between environmental factors and the immune system.[4]

Chronic rhinosinusitis is a health problem that affects 5–12% of the world's population, affects the quality of life, and costs quite a lot. In America, 13% of the total population suffers from chronic rhinosinusitis, and in Europe, about 10.9% of the population suffers from chronic rhinosinusitis, with an incidence of 1.13:100 people per year. From the data in 2020, rhinosinusitis is the most common disease found in the outpatient clinic of ORL-HNS in RSSA Malang, which is 56%.[1,3]

Traditionally, chronic rhinosinusitis is divided into chronic rhinosinusitis with nasal polyps (CRSwNP) 20%, and chronic rhinosinusitis without nasal polyps (CRSsNP) 80%. However, differences in pathophysiology and mechanisms have not been clearly defined.[2,3,5] Recent research suggests differences in immunological mechanisms in the form of endotypes between CRSwNP and CRSsNP.[6] The immune response in chronic rhinosinusitis is divided into three types, namely, the type I immune response targets the virus with the main endotype being IFN-γ, the type II response targets the parasite with the main endotype being Charcot-Leyden Crystal Galectin (CLC) mRNA or eosinophil cationic protein (ECP). Type III immunity targets extracellular bacteria and fungi, with the main endotype being IL-17A.[3,7] Some guidelines divide chronic rhinosinusitis into two phenotypes, CRSwNP and CRSsNP. It is based on a different endotype, which CRSwNP have the characteristics of Th2-mediated eosinophilic inflammation, which will produce cytokines such as Il-4, IL-5, and IL-13, so they are dominated by type II inflammation. On another side, CRSsNP has neutrophilic inflammation characteristics,

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which is Th1-mediated, which produces the cytokine interferon-gamma (IFN-γ) so that it is dominated by inflammation types I and III.[3,8–10]

Recent research has focused on the inflammation that occurs and develops in sinus tissue, where the main focus is on identifying molecular pathways or endotypes. In recent decades, understanding endotypes in chronic rhinosinusitis has led to a focus on managing chronic rhinosinusitis based on the inflammatory biomarkers that underlie this disease and how these biomarkers respond to treatment. Appropriate medical therapy includes topical or oral corticosteroids, nasal irrigation with saline, and monoclonal antibody therapy. In addition, there is also surgical therapy, but the best time for surgery is still debated now. Investigations that can be done in chronic rhinosinusitis can be in the form of endoscopy and CT scan; it is also necessary to examine allergies interconnected with chronic rhinosinusitis. Assessment of quality of life is also essential to be assessed as the most affected aspect of chronic rhinosinusitis.[3]

Neutrophils or polymorphonuclear leukocytes are the most abundant leukocytes in the blood and have an essential function in early phagocytosis and killing microbes in the extracellular mucosa. The role of neutrophils in the pathophysiology of chronic rhinosinusitis remains unclear. Still, neutrophil activation is associated with microbial infection or tissue damage signals and IL-8 release in the epithelium, and neutrophil levels tend to be high in almost all cases.[3,10] Eosinophils have an essential role in tissue repair and immune defense, especially against helminths. Eosinophils are also a critical cell type in asthma, allergic rhinitis, and chronic rhinosinusitis. Eosinophilic-induced damage to the sinonasal mucosa is believed to be the primary pathophysiological mechanism. Although the pathological effect of eosinophil activity on chronic rhinosinusitis is unclear, it is possible that eosinophil degranulation causes tissue edema, epithelial damage, and possibly fibrosis, as is the mechanism in asthma. Eosinophils have also been shown to exert a protective effect on the immune system against bacteria at the site of barrier damage.[3]

Identifying the type of inflammation of chronic rhinosinusitis based on NER allows the clinician to know the pathophysiological differences that occur and allow for differences in the administration of therapy to be more effective and have better results. This study aims to prove that NER in CRSsNP will be higher than that in CRSwNP, and the inflammatory type that is more dominant in CRSwNP is the eosinophilic type, while in CRSsNP is the neutrophilic type.

Materials and Methods

This study was an observational analytic study with a cross-sectional approach to compare the NER in CRSwNP and CRSsNP patients at the clinic of ENT Saiful Anwar Hospital Malang, Indonesia. This study passed the ethical test and was conducted in January–October 2017. Sampling in this study used a consecutive sampling technique. The research sample was CRSwNP or CRSsNP who came for treatment at the outpatient clinic of ENT in Saiful Anwar Hospital Malang and met the inclusion and exclusion criteria.

The inclusion criteria in this study were patients aged more than or equal to 18 years at the time of the study who experienced symptoms of chronic rhinosinusitis in the form of two symptoms, one of which was nasal congestion or nasal discharge and other symptoms such as facial pain and reduced or loss of smell ability for 12 weeks. Supported by endoscopic examination with the results of nasal polyps and mucopurulent secretions from the middle meatus, edema, and mucosal obstruction in the middle meatus, also on a CT scan, it was found that there were changes in the osteomeatal complex and sinus and evidenced by the results of the examination. In addition, patients were also willing to participate in the study by signing an informed consent to participate in the study after receiving an explanation. The exclusion criteria were if the study subjects had received systemic corticosteroid therapy or systemic antibiotics for 7 days or topical corticosteroid therapy for 30 days.

Patients with chronic rhinosinusitis who met the inclusion and exclusion criteria and were willing to participate in the study would undergo surgery with anterior antrostomy, which could be performed under general or local anesthesia by the Supervisor Doctor of the Rhinology Division, Department of ENT in Saiful Anwar Hospital Malang. The maxillary sinus mucosal tissue specimen was taken, then stored in a sterile container during the surgery. During the transport of the specimen by using a cooler, the neutrophil and eosinophil cell count would then be examined using BioLegend® Neutrophil and Eosinophil Kit Flow Cytometry which was carried out at the Physiology Laboratory Faculty of Medicine Universitas Brawijaya, Malang. The normal level of eosinophils in the paranasal sinus mucosal tissue was 0.3–0.7% of the total cells, and the normal level of neutrophils in the paranasal sinus mucosal tissue was 1.1–1.7%. NER was calculated based on neutrophil levels divided by eosinophil levels. The normal NER limit in the paranasal sinus tissue was 2.8. If it was higher than this limit, it included neutrophilic inflammation, and if it was less than this limit, it included eosinophilic inflammation.[11,12]

All data obtained were processed using the Statistical Package for the Social Sciences (SPSS) 23.0.0 program. Data on gender, education, chief complaint, and type of inflammation, including categorical data, were described in percentage form. Data for age, percentage of neutrophils, and eosinophils were numerical data carried out by the Kolmogorov–Smirnov test to see the data distribution. If the data were obtained in a normal distribution, it was described as mean + standard deviation. However, if the data distribution was not normal, it was described as median + interquartile range. Statistical analysis of NER in CRSwNP and CRSsNP used student *t*-test if the distribution was normal.

Results

The study found 24 patients with chronic rhinosinusitis based on inclusion and exclusion criteria, then divided them into CRSwNP and CRSsNP.

Table 1 presents the general characteristics of this study. CRSwNP was more common in men (58.33%) than in women (41.67%), while in CRSsNP, the incidence was similar between men and women by 50%. When compared in age, CRSwNP was more common in older people with a mean age of 47.67 ± 11.32 compared with CRSsNP with a mean age of 37.17 ± 14.77. The research data found that the level of education of both patients with CRSwNP and CRSsNP was higher in patients with education in the low category. The main complaint dominant in the CRSwNP patients in this study was nasal congestion and as many as 10 people had this complaint (83.33%), and there were two people (16.67%) with the main complaint of nasal discharge. Meanwhile, in patients with CRSsNP, the main symptoms of complaint varied, with the most frequent complaints being nasal congestion and as many as five people had (41.67%), four people had facial pain as complaint (33.33%), and nasal discharge was shown by as many as three people (25%).

Table 1: General characteristics of research subjects

	CRSwNP		*CRSsNP*	
Gender (*n*, %)				
Man	7	58.33	6	50
Woman	5	41.67	6	50
Age				
(years, mean ± SD)	12	47.67 ± 11.32	12	37.17 ± 14.77
Education (*n*, %)*				
High	5	41.67	4	33.33
Low	7	58.33	8	66.67
Chief complaint (*n*, %)				
Nasal congestion	10	83.33	5	41.67
Nasal discharge	2	16.67	3	25
Facial pain	0	0	4	33.33
Hiposmia	0	0	0	0

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; High: graduated from high school and above; low education, did not go to school until they finished junior high school; SD, standard deviation

Table 2: Comparison of neutrophil, eosinophil, and NER in tissues

	CRSwNP		*CRSsNP*		
	n	%, *mean* ± *SD*	*n*	%, *mean* ± *SD*	*p*
Neutrophils	12	5.31 ± 0.24	12	4.29 ± 2.42	0.282
Eosinophils	12	4.76 ± 2.55	12	3.60 ± 2.88	0.311
NER	12	1.33 ± 0.71	12	2.58 ± 3.07	0.196

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; SD, standard deviation

Table 3: Types of inflammation in tissues

	CRSwNP		*CRSsNP*	
	n	%	*n*	%
Neutrophilic	2	16.67	2	16.67
Eosinophilic	10	83.33	10	83.33

CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps

Table 2 presents an examination of the eosinophil and neutrophils counts from the mucosal tissue of the maxillary sinus performed. The mean result of neutrophils in the CRSwNP was 5.31 ± 0.24, and in the CRSsNP, it was 4.29 ± 2.42. There was no significant difference ($p = 0.282$). For the number of eosinophils in the mucosal tissue, the average CRSwNP was 4.76 ± 2.55. The average of CRSsNP was 3.60 ± 2.88, so there was a nonsignificant difference ($p = 0.311$) in the number of eosinophils in CRSwNP and CRSsNP. After knowing the number of neutrophils and eosinophils in tissue, NER was calculated with the average CRSwNP of 1.33 ± 0.71 and the average CRSsNP of 2.58 ± 3.07. From the NER calculations, there were no significant differences ($p = 0.196$). From the results of the NER, we can determine the dominant type of inflammation in the tissue.

Table 3 depicts that the dominant type of inflammation in CRSwNP and CRSsNP was eosinophilic inflammation; as many as 10 people (83.33%) were similar in each group. This study found no significant differences in NER and type of inflammation between CRSwNP and CRSsNP.

Discussion

Chronic rhinosinusitis is an inflammation involving the paranasal sinuses and nose that lasts longer than 12 weeks. At least two symptoms must be present, one of which is nasal congestion or nasal discharge, and the other, such as facial pain and reduced or loss of the ability to smell. In addition, an endoscopic examination may reveal nasal polyps and mucopurulent secretions from the middle meatus, mucosal edema, and obstruction in the middle meatus. A CT scan may reveal the changes in the osteomeatal complex and sinuses.[3,8]

The prevalence of CRSwNP is more common in men and mature age than in CRSsNP. Won et al.[13] found that the prevalence of CRswNP increased with age; the median age of CRSwNP was above 40 years, while CRSsNPs were more common under 40 years of age. CRSwNP was more common in men, smokers, and a high Body mass index (BMI) and was often associated with asthma. Brescia et al.[14] found that recurrence of nasal polyps in the elderly was less common than in young adults. It was associated with less eosinophil infiltration and more allergic patients in young adults than in the elderly.

In this study, the level of education in patients with CRSwNP and CRSsNP was more common with low education. Following research conducted by Geramas et al.[1] found that the relationship between education level and chronic rhinosinusitis was somewhat difficult to explain, but education level was associated with lower socioeconomic status, so access to health facilities was difficult. In addition, research by Kilty et al.[15] found that CRS patients' level of education was low, and the symptoms were more severe in rhinosinusitis patients.

The division of CRSwNP and CRSsNP phenotypes were distinguished based on examination findings and the pathophysiology. Research conducted by Talat et al.[16] showed that the main symptoms found in CRSwNP were nasal congestion and hyposmia, while in CRSsNP, it was more varied, and facial pain symptoms were the more common symptoms. This study also concluded that CRSsNP patients had poorly nasal quality, but CRSwNP patients had disturbing symptoms.

The immune response in chronic rhinosinusitis is based on a physiological immune response against pathogens as they cross the mucosal barrier, which will cause a cellular response and the release of cytokines, causing an inflammatory process. The immune response in chronic rhinosinusitis is divided into three types: the type I immune response targets the virus with the main endotype being IFN-γ, and the type II response targets the parasite with the main endotype Charcot-Leyden Crystal Galectin (CLC) mRNA or ECP. Type III immunity targets extracellular bacteria and fungi, with the main endotype being IL-17A.[3,7]

In chronic rhinosinusitis, type II immune response, mast cell activation, eosinophil activation, and plasma cell activity occur. It causes the emergence of clinical symptoms related to the healing process of sinonasal tissue, leading to the formation of polyps, goblet cell hyperplasia, and abnormalities of the epithelial barrier. The healing process will cause increased permeability of the epithelial barrier and the possibility of persistence or recurrence. These changes are most clearly seen in chronic rhinosinusitis type II immune response. The symptoms will be more severe, the treatment failure rate will be higher, and the recurrence rate will be more elevated.[3,4]

Some guidelines divide chronic rhinosinusitis into two phenotypes: with nasal polyps and without nasal polyps. It is based

on a different endotype where CRSwNP has the characteristics of Th2-mediated eosinophilic inflammation, which will produce cytokines such as Il-4, IL-5, and IL-13. It is dominated by type II inflammation. While CRSsNP has the characteristics of Th1-mediated neutrophilic inflammation, which is characterized by Th1-mediated neutrophilic inflammation producing the cytokine interferon-gamma (IFN-γ) so that it is dominated by non-type II inflammation. This division correlates with patient management outcomes, where CRSwNP requires surgical therapy. Chronic rhinosinusitis with polyps is more likely to lead to an eosinophilic process, whereas chronic rhinosinusitis without polyps is more likely to lead to a neutrophilic process.[3,8–10]

Stevens et al.[7] found that CRSwNP and CRSsNP were closely related to type II inflammation dominated by eosinophils, and facial pain symptoms in CRSsNP were also associated with type II inflammation. Delemarre et al.[5] found that 49% of patients with CRSsNP exhibited type II immune response. Still, the type II inflammation in CRSsNP was weaker, with an absolute number of infiltrating eosinophils 18 times lower than that in CRSwNP. CRSsNP with a type II immune response also decreased IL-17 levels. The weaker type II immune response in CRSsNP causes a lower recurrence rate in CRSsNP than in CRSwNP. In this study, the type II immune response in CRSsNP was also associated with a history of atopy and asthma. A small proportion of the study subjects showed tissue development toward nasal polyps.

The increasing number of studies on chronic rhinosinusitis proves that there is much overlap between the chronic rhinosinusitis phenotype and the existing immunological profile. It can happen because of the complexity of the pathophysiology; there are variations in each individual, such as the immune system, genetics, and environmental factors, such as infection.[8] Lal et al.[2] found that although the involvement of eosinophils in CRSsNP was considered low, some patients had evidence that the predominant inflammatory factor was eosinophils. This study supports the notion that the pathogenesis of CRSsNP may not be a "black or white" distinction between types of inflammation. These findings also corroborate previous attempts to classify CRSsNP according to eosinophilic chronic rhinosinusitis (ECRS) and non-eosinophilic chronic rhinosinusitis (NECRS). In this study, patients with ECRS had more severe symptoms than patients with NECRS. According to Tecimer et al.,[17] the level of eosinophils in the tissue can be used as a therapeutic and prognostic parameter. The higher the level of eosinophils, the worse the prognosis and the higher incidence of disease recurrence. In addition, another reason that can cause the dominance of eosinophils in CRSsNP is that patients have a history of atopy, which is usually associated with tissue eosinophils. Many CRSwNP and CRSsNP patients show a mixed neutrophilic–eosinophilic TH1–TH2 pattern of inflammation. It explains why patients with CRSsNP may benefit from medical and surgical therapeutic interventions that are conventionally directed mainly to CRSwNP and why some patients with CRSsNP respond well to oral corticosteroids. It supports the shift to more precise chronic rhinosinusitis therapy.[2,3]

Conclusion

Based on the results of this study, there was no significant difference between NER and the type of inflammation between CRSwNP and CRSsNP. Further research is needed regarding what factors influence the growth of nasal polyps because the presence of nasal polyps is associated with chronic rhinosinusitis that is difficult to treat.

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