Differences of Daytime Nasal Symptoms Score and Nighttime Symptoms Score Between the Combination of Montelukast with Loratadine and Single Loratadine in Allergic Rhinitis (Meta-Analisis)

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Abstract
Background: The success of allergic rhinitis (AR) therapy has not yet been achieved because 76% of patients with AR still experience symptoms of nasal obstruction despite receiving oral AH. The symptom of a blocked nose at night is the most disturbing in 80% of patients with AR. Complaints of nasal congestion that persist after administration of AH are associated with swelling of the nasal mucosa caused by cysteine leukotrienes (CystLTs). The severity of AR symptoms can be assessed by the daytime nasal symptoms score (DNSS) and nighttime symptoms score (NSS). **Objective**: To know the difference between DNSS and NSS between the combination of montelukast and loratadine and single loratadine in patients with AR. **Methods**: Meta-analytical study, with Science Direct database, PubMed central and publisher website, Cochrane library, ResearchGate, and SAGE journals, year of publication limited to the last twenty-five years, randomized controlled trial, comparison single loratadine. DNSS and NSS differences assessment is based on the mean difference (MD). Test for heterogeneity using RevMan 5.4. **Results**: The search for articles found 777, with 3 articles meeting the eligibility criteria, 3 assessment articles based on DNSS and two articles based on NSS. The use of the combination of montelukast and loratadine did not show a significant reduction in DNSS (MD -0.11; 95% CI -0.25 to 0.03; p=0.13; I^2=73%) and show a significant reduction in NSS (MD -0.05; 95% CI -0.10 to -0.00; p=0.004; I^2=37%). **Conclusion**: There was no difference in DNSS between montelukast and loratadine combined with single loratadine in AR patients. There was no difference in NSS between montelukast and montelukast loratadine combined with single loratadine in AR.

Keywords : Allergic rhinitis, montelukast, loratadine, daytime nasal symptoms score, nighttime symptoms score

1. Introduction

Allergic rhinitis (RA) is a worldwide health problem; this disease has a negative impact on the patient's quality of life and can cause economic and social issues [1][2]. RA therapy includes avoiding allergen exposure, pharmacotherapy, and immunotherapy. RA pharmacotherapy includes oral antihistamines (AH), intranasal AH, decongestants, leukotriene receptor antagonists (ARLT), intranasal corticosteroids (KIN), and cromolyn sodium [3]. The success of RA therapy at this time has not been achieved because 76% of RA patients still experience symptoms of nasal congestion even though they have received oral AH [4]. The sign of a blocked nose at night is the most disturbing in 80% of patients with RA [5].

Loratadine is one of the AH that is often used; the second generation has minimal side effects. This drug cannot eliminate all the symptoms of RA, especially the symptoms of a blocked nose, so it is often

combined with other drugs [6]. Intranasal corticosteroids are superior in reducing the symptoms of RA. Still, in some patients, poor adherence rates are found because of the way they are used, so other alternative drugs are needed [5]. Complaints of persistent nasal obstruction after administration of AH related to swelling of the nasal mucosa caused by cysteine leukotrienes (CystLTs) [7]. Until now, research on the efficacy of using ARLT as therapy in RA patients at the Outpatient Unit (URJ) Ear Nose Throat Head and Neck Surgery (ENT-KL) Regional General Hospital (RSUD) Dr. Soetomo Surabaya has never been done.

Leukotriene receptor antagonists are the treatment of choice for patients with RA that can be used for all degrees of RA, namely intermittent and persistent mild or moderate-severe degrees. Leukotriene receptor antagonists were included in the ARIA therapy guidelines for RA in 2008 [3]. Leukotriene receptor antagonist drugs used in Indonesia are montelukast and zafirlukast [8]. Montelukast is an ARLT drug that is often used to treat RA. This drug is a CysLTs type 1 receptor antagonist found on immunocytes, smooth muscle and endothelium of the respiratory mucosa [4].

The prevalence of RA reaches 10-20% in the world population and is expected to continue to increase [9]. Electronic medical record (EMR) data for RA cases at RSUD Dr. Soetomo Surabaya showed the number of new cases of RA in 2017 which was 106 (36%) cases, old cases 189 (64%) cases. The number of new cases of RA in 2018 was 124 (37%) cases, 212 old cases (63%) cases. The number of new cases of RA in 2019 was 100 (36%) cases, old cases 177 (64%) cases [10]. Assessment of the severity of RA symptoms can be determined by the daytime nasal symptoms score (DNSS) and nighttime symptoms score (NSS) [11] [12].

2. Method

This type of research is a meta-analysis research. The research problem is explained using population, intervention, comparison, outcome, and study design (PICOS). The population includes RA patients with positive SPT results or positive specific IgE, age ≥15 years, and patients with asthma or not. The inclusion criteria were a randomized controlled trial (RCT) study design, the final evaluation must include DNSS and NSS, the data displayed the mean ± standard deviation (SD) or mean, the upper and lower limits of the confidence interval, and the sample size. Exclusion criteria were articles that still allowed the use of KIN, research reports in languages other than English and Indonesian, and incomplete data. Intervention is giving montelukast and loratadine. The outcome of this research is DNSS and NSS. Study design randomized controlled trial using mean difference (mean±SD). The search for research articles on Science Direct, PubMed central and publisher website, Cochrane library, ResearchGate, and SAGE journals was carried out for two months, from November to December 2021. The search strategy used the Booelan operator, namely: montelukast OR "leukotriene receptor antagonist" OR antileukotriene OR "leukotriene inhibitor") AND

"allergic rhinitis" AND "loratadine". Critical appraisal is assessed based on the CASP RCT Checklist 2018. The research steps are based on the PRISMA 2020 flow diagram.

Montelukast is a CysLTs type 1 receptor antagonist. Montelukast blocks the activity or secretion of CysLT1 which acts as a potent inflammatory mediator associated with nasal obstruction, mucus production, and inflammatory cell recruitment. The dose used in the study in the article was 10 mg once daily for 14 days. Loratadine is a second-generation histamine H1 receptor antagonist. Loratadine competitively inhibits the interaction of histamine with H1 receptors. The dose used in the study in the article was 10 mg once daily for 14 days. Daytime nasal symptoms score is the average of the sum of each nasal symptom, namely: sneezing, itchy nose, runny nose, and nasal congestion using a four-point scale, namely 0-3. The average score that can be obtained is a minimum of 0 and a maximum of 3. Nighttime symptoms score is the average score obtained from the score of difficulty initiating sleep, frequent awakening during sleep, and nasal congestion when awakening. Score scale from 0-3 for each symptom. The average score that can be obtained is a minimum of 0 and a maximum of 3.

Processing and analysis with Cochrane Collaboration using RevMan 5.4 which shows effect size, heterogeneity test, and test for overall effect. This study has a significance level (α) of 0.05 or 5%.

3. Result

The article search obtained 777 research articles through five electronic databases. There were 3 articles for critical appraisal (Figure 1), and 3 research articles with a publication year span of 2000-2009 that met the requirements for data analysis (Table 1).[11,13,14] Three articles totaled 566 subjects in the group. combination of montelukast and loratadine and 509 in the loratadine group alone. The age of the sample in this study was 15-85 years. Follow-up in this study was 2 weeks in all articles.

Tabel 1. CASP RCT Checklist

Peneliti Tahun	**CASP checklist**											**Score**
	Section A			Section B				Section C				
	1	2	3	4	5	6	7	8	9	10	11	
Meltzer, *et al*., 2000	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	10
Nayak, *et al*., 2002	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	10
Lu, *et al*., 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11

Ket: *Section A: are the result of the study valid?; Section B: What are the result?; Section C: Will the results help locally?; Y= Yes; N= No; ? = Can't tell*

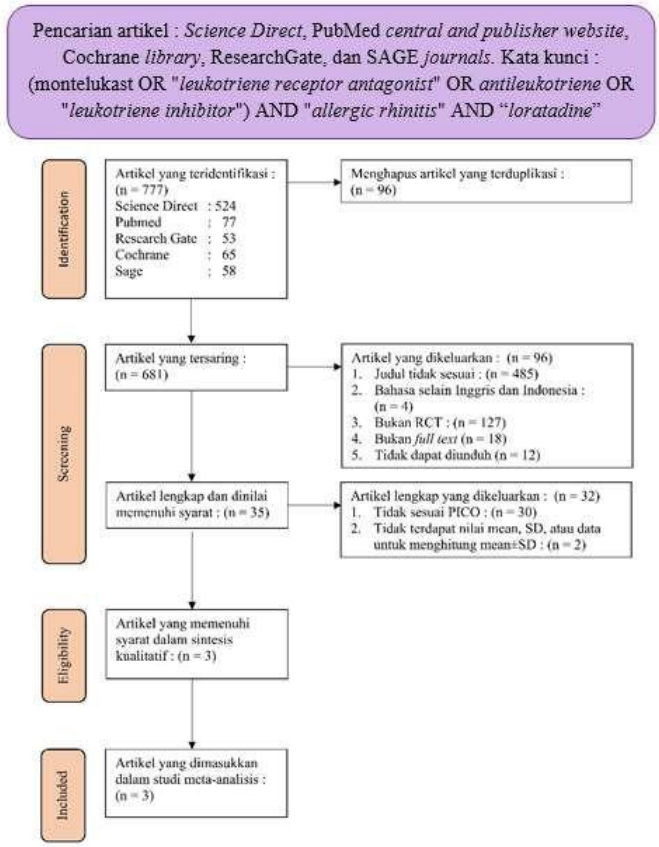

Figure 1. Literature search flow using PRISMA 2020

a. The mean±SD, forest plot, funnel plot of the difference in DNSS between the combination of montelukast and loratadine with loratadine alone.

The largest sample size in the study of Nayak, et al., as many as 292 samples using loratadine, while the lowest sample size in the study of Meltzer, et al., 86 samples using montelukast and loratadine. The highest scale of DNSS improvement in the montelukast and loratadine combination group was in the study of Lu, et al., with a value of -0.54±0.6 and the lowest was in the study of Meltzer, et al., with a value of -0.61±0.513. The highest scale of improvement in DNSS in the loratadine group was in Meltzer et al.'s study, with a value of -0.34±0.469 and the lowest was in Lu et al.'s study, with a value of -0.53±0.56.

The results of the analysis showed high heterogeneity between research articles (I2=73%), so the random effect method was used. The interpretation of the results showed that the use of montelukast and loratadine did not reduce DNSS compared to the administration of loratadine alone in RA patients which was not statistically significant (p= 0.013; SMD -0.11; 95% CI -0.25 to 0.03). The funnel plot shows that the right and left side plots are not symmetrical to each other, do not form an inverted funnel, and there is an imbalance in the distance between research articles on the left and right sides. This indicates that in this study there is a large publication bias.

b. Mean±SD, forest plot, funnel plot of NSS difference between montelukast and loratadine combination with loratadine alone.

The largest sample size in the study of Nayak, et al., as many as 292 samples using loratadine, while the lowest sample size in the study of Meltzer, et al., 86 samples using montelukast and loratadine. The highest scale of improvement in NSS in the montelukast and loratadine combination group in the study of Meltzer et al., with a value of -0.33 ± 0.48. The highest scale of improvement in NSS in the loratadine group was in the study of Meltzer, et al., with a value of -0.19±0.516.

The results of the above analysis show low heterogeneity between research articles (I2=37%), so the fixed effect method is used. The interpretation of the results showed that the use of a combination of montelukast and loratadine could reduce NSS in patients with RA which was statistically significant (p= 0.004; SMD -0.05; 95% CI -0.10 to -0.00). The funnel plot forms an inverted funnel and the distance between the research articles on the left and right is relatively balanced. This indicates that in this study the publication bias is not large.

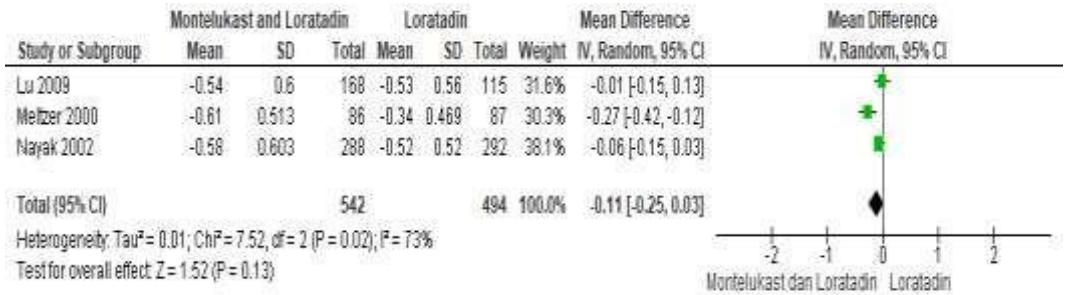

Figure 2. Forest plot of the difference in DNSS between the combination of montelukast and loratadine with loratadine alone.

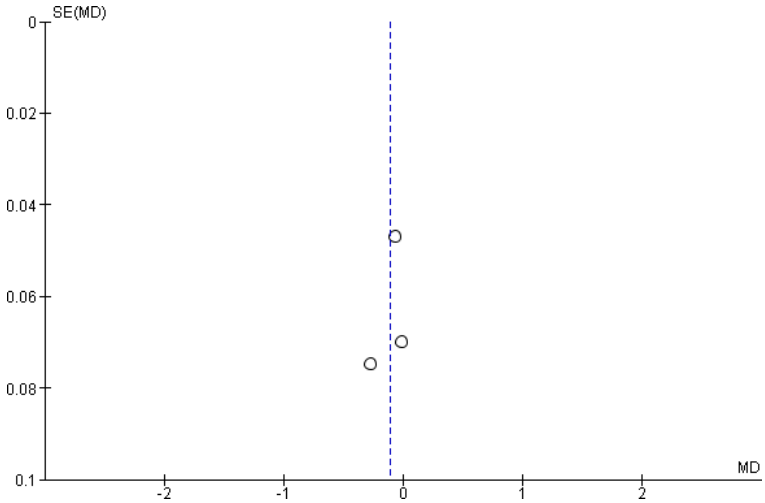

Figure 3. Funnel plots the difference in DNSS between the combination of montelukast and loratadine with loratadine alone.

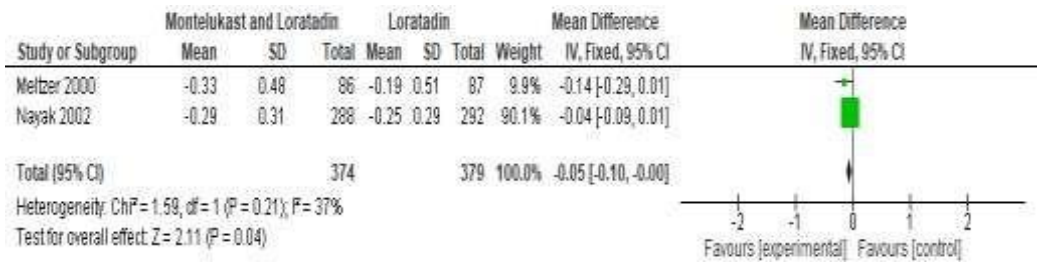

Figure 4. Forest plot of NSS differences between the combination of montelukast and loratadine with loratadine alone.

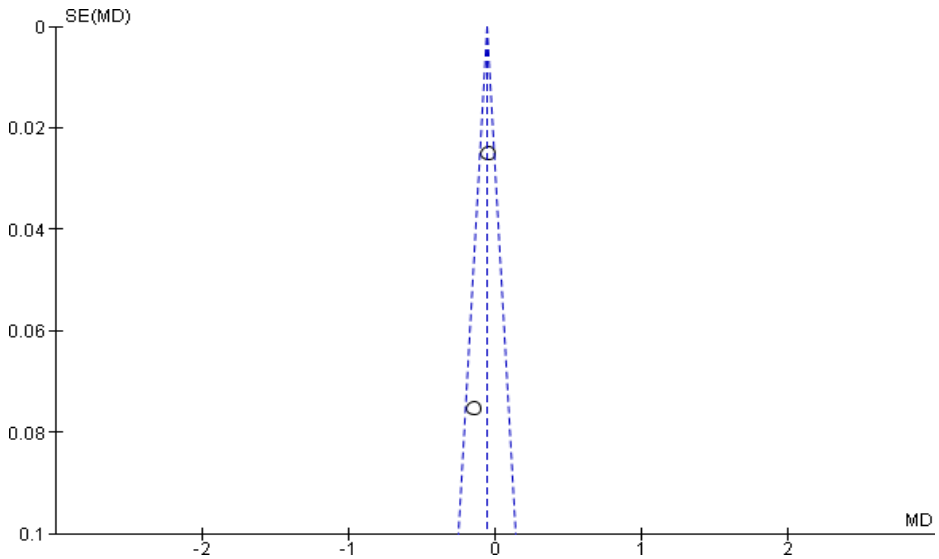

Figure 5. Funnel plot of NSS difference between montelukast and loratadine combination with loratadine alone

4. Discussion

Montelukast was initially developed to treat asthma, but nowadays, it is also used to treat RA. Montelukast inhibits the action of cysteinyl leukotrienes (CysLTs) by blocking CysLT type 1 receptors on the respiratory mucosa, so mucus production, mucosal lining, inflammation, and airway infiltration eosinophils, and maturation of dendritic cells does not occur, which triggers RA[4]. This drug has no significant side effects, does not cause sedation, is taken once a day, and can be used for ages older than six months[15].

The three study articles meeting the inclusion and exclusion criteria were all from the United States. The sample size was 566 patients in the montelukast and loratadine combination group, whereas 509 patients were in the single loratadine group. The sample was dominated by women, 677 patients (62.97%), then men, 398 patients (37.02%), with an overall ratio of women: to men was 1.7:1. This is following a meta-analysis conducted by Pinart et al., regarding the prevalence of RA by gender, male predominant RA patients at the age of children, but at puberty, female RA sufferers. Several hypotheses explain the existence of gender differences in the prevalence of RA, including differences in immune response status, physiological changes during puberty such as endogenous and exogenous hormones, lifestyle, use of cosmetics, and daily activities [16].

The heterogeneity test of the three research articles on DNSS was found to be 73%, meaning that the

three articles were heterogeneous. The test for overall effect and the confidence interval depicted in the forest plot showed no statistical significance (p>0.05), which means that using a combination of montelukast and loratadine did not reduce DNSS compared to the administration of loratadine alone in RA patients. This insignificant analysis could be due to differences in the number of samples in research articles where the number of articles showing statistically insignificant is much larger than articles showing significant changes. It can cause a type of selection bias in publications called publication bias [17].

Another meta-analysis by Liu et al., evaluating the difference in DNSS between the combination of montelukast and antihistamines with a single antihistamine, found that the combination of montelukast and antihistamines was associated with a decrease in DNSS (SMD -0.11, 95%CI: -0.19 to - 0.03, p=0.009; I2=31%). In this study, the antihistamines used included loratadine, cetirizine, levocetirizine, and fexofenadine. The duration of the evaluation varies between 2-6 weeks. Oral antihistamines that block H1 receptors effectively reduce sneezing, rhinorrhea, and nasal itching but are less effective at treating nasal congestion [18].

Wilson et al. investigated the difference in DNSS between combinations of other antihistamines, cetirizine and montelukast, with cetirizine alone. The results of the analysis showed a statistically significant decrease in DNSS in the combination of montelukast and cetirizine compared to cetirizine alone. Cetirizine, a second-generation antihistamine, is known to show greater improvement in RA symptoms than loratadine administration [19].

Publication bias in the study was determined from the distribution of the funnel plot, namely the scatter diagram in the meta-analysis, to detect the possibility of publication bias visually. This study found a large publication bias with asymmetric distribution of the funnel plot on the right and left sides, as well as an imbalance in the distance between articles. The funnel plot shows the relationship between the study's effect size and the sample size of various studies, which are measured in different ways [15]. The impact of this publication bias is that the results or information produced are not optimal because the published literature may not represent the research that has been done on a topic [20].

The heterogeneity test of the two research articles on the difference in NSS was found to be 37%, meaning that the two articles were homogeneous. The test for overall effect and the confidence interval depicted on the forest plot showed statistical significance (p=0.04), which means that using a combination of montelukast and loratadine reduced NSS compared to the administration of loratadine alone in RA patients. *Cysteinyl leukotrienes C4, D4, and E4,* are important mediators of airway inflammation that also play a role in the pathogenesis of RA. For example, in the nasal lavage of RA patients, high CysLTs were found, where the CysLTs caused nasal obstruction and rhinorrhea. Nasal obstruction is the most disturbing symptom of RA at

night, causing a decrease in sleep quality [11].

Another meta-analysis study also obtained similar results. There was a statistically significant reduction in NSS between the combination of montelukast and antihistamines compared to a single antihistamine (SMD -0.16, 95%CI: -0.28 to 0.01, p=0.006; I2=0%). In this study, the antihistamines used were loratadine and levocetirizine. Evaluation duration varies between 2-6 weeks [5].

A study reported in Thailand on 115 RA patients found that montelukast combined with loratadine reduced NSS significantly compared to loratadine alone. The study was conducted on children aged 6-15 years. A delayed-phase allergic reaction in the form of nasal obstruction is found in 50% of patients with RA. Cysteinyl leukotrienes play an essential role in delayed-phase allergic reactions by increasing vascular permeability, tissue volume, mucus secretion, and inflammatory cell recruitment. Antihistamines effectively control complaints of sneezing, runny nose, and itchy nose but do not reduce eosinophils, so that nasal congestion still occurs [7].

Publication bias in the study was determined from the distribution of the funnel plot, namely the scatter diagram in the meta-analysis, to detect the possibility of publication bias visually. This study forms an inverted funnel. The distance between research articles on the left and right sides is relatively balanced, indicating that this study's publication bias is not large. Research with a low publication bias is considered higher quality and can be used as a guide [20].

This study has several limitations, including the number of articles discussing the administration of a combination of montelukast and loratadine in patients with RA. In addition, there are no recent journal publications that meet the inclusion and exclusion criteria of the study and limited research articles from the United States.

5. Conclusion

There was no difference in the daytime nasal symptoms score between the combination of montelukast and loratadine and loratadine alone in patients with allergic rhinitis. There was no difference in the nighttime symptoms score between the combination of montelukast and loratadine and loratadine alone in allergic rhinitis.

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