The Effectiveness Comparison of Desloratadine and Loratadine in Reducing Total Nasal Symptom Score and the Level of Interleukin 4 in the Nasal Secretions of Allergic Rhinitis Patients

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Abstract

Background: Allergic rhinitis (AR) is a common atopic disease; however, the available therapy has limitation in the usage and its success rate. Desloratadine has a role as an alternative allergic rhinitis therapy to eliminate the overall symptoms of AR and reduce IL-4 level in nasal secretions.

Method: This study was double-blind randomised clinical trial with pre-post test design. The data was analyzed by using independent sample t-test**.** There were 24 AR patients divided into 2 therapy groups which were study group (desloratadine) and control group (loratadine). The evaluation based on SGHT and IL-4 in nasal secretions was conducted pre and post 15 days of therapy.

Results: The present study that was conducted on July-October 2016 showed significant difference in the average percentage of reduced TNSS in desloratadine group compared to loratadine group (p=0.000). The comparison of reduced level of IL-4 in nasal secretions between desloratadine and loratadine group was indicated insignificantly different.

Conclusion: Reduced TNSS in desloratadine group was higher than in loratadine group. Also, there was no difference in decreased level of IL-4 in nasal secretions.

Keywords: *Desloratadine, loratadine, total nasal symptom score, interleukin 4, allergic rhinitis.*

Introduction

Allergic rhinitis (AR) is a common inflammatory nasal mucosal disease mediated by Immunoglobulin E (Ig E) after the exposure of allergen in nasal mucosa. The main symptoms of AR include sneezing, stuffy nose, runny nose, and itchy nose. Several cases of AR are accompanied by the occurrence of symptoms in eyes, ears, and post nasal drip in throat [1]. The assessment of AR symptom severity is determined by total nasal symptom score (TNSS) [2]. The clinical manifestations of AR involve proinflammatory cytokines and other cytokines; one of the essential cytokines in AR is Interleukin 4 (IL-4) which has a role to form Ig E and recruit eosinophils.

Loratadine is an H1-antihistamine that has not been able to eliminate the overall symptoms of AR; therefore, the use of loratadine is often combined with other drugs. Desloratadine is an active metabolite from loratadine known to have more potent affinity towards H1 receptor than loratadine itself. It also can reduce the level of IL-4 in AR [3]. The high severity of AR encourages researchers to reveal other AR therapies beside loratadine. However, it has not been conducted any study that compares the effectiveness of desloratadine and loratadine in reducing TNSS and IL-4 level of nasal secretions in AR patients in Department of Otolaryngology-Head and Neck Surgery,

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The latest research proved that desloratadine was an active metabolite from loratadine and as a single therapy to eliminate AR symptoms especially stuffy nose and reduce IL-4 level in nasal secretions [4]. Desloratadine is the main active metabolite from loratadine that can decrease either nose symptoms or other symptoms such as chronic idiopathic urticaria [5]. Another in vitro research also showed that the affinity of desloratadine towards H1 receptor was 50-194 times bigger than loratadine, cetirizine, and fexofenadine [6]. Another study also stated that in 2 weeks, AR patients who consumed desloratadine 5mg/day has a significant impact in decreasing stuffy nose than placebo ($p<0,05$) [7].

One of the cytokines from Th2 that plays an important role in AR pathophysiology is IL-4. The role of IL-4 is to produce and differentiate B cell to be plasma cell [8]. Afterwards, it will produce Ig E that is tied to mast cell and basophile. In addition, another role of IL-4 is to competitively impede or produce cytokines from Th1. It also has a role in recruiting eosinophil which is connected to vascular cell adhesion molecul-1 (VCAM-1) [2]. The activation of eosinophil causes chemical mediator extrication such as mayor basic protein (MBP), eosinophil cationic protein (ECP) and eosinophil peroxidase (EPO). This chemical mediator causes clinical manifestation such as sneezing, runny nose, itchy, and stuffy nose [9]. A particular research revealed that the total of IL-2, IL-4, IL-13 cytokines and TNF-α in nasal secretions was significantly higher ($p<0.05$) rather than the total number in serum. IL-4 significantly increases in AR patients compared to non AR patients [10]. Based on the elaboration above, the researcher is intended to conduct a study to compare the effectiveness of desloratadine and loratadine to reduce TNSS and IL-4 level in nasal secretions in AR patients.

Method

The research subjects were moderate-severe intermittent AR patients, mild intermittent AR patients and mild persistent AR patients based on ARIA 2008 who were treated in Outpatient Otolaryngology-Head and Neck Surgery Unit, Division of Immunology-Allergy, Dr. Soetomo General Hospital Surabaya and fulfilled inclusion and exclusion criteria. The inclusion criteria were pre therapy TNSS more than or equal to 5, aged 21-60 years old, have not consumed anti allergic drugs such as: AH (1 week), systemic corticosteroids (4 weeks), topical corticosteroids (2 weeks), topical decongestants (1 week), anticholinergic and chromoline, willing to follow the research and signed the consent forms. The exclusion criteria were acute respiratory tract infections, acute and chronic paranasal sinusitis, medical rhinitis, nasal abnormalities such as tumors, rice polyps, severe deviation septum, pregnancy or lactating and a history of loratadine allergy.

This study was conducted by employing double-blind randomized controlled trial with pre-post test design [11]. The sample collection was conducted by using the method of consecutive sampling on July-October 2016. The samples were allocated randomly based on block permutation technique which was divided into study group and control group. The study group obtained desloratadine therapy 5 mg/day while the control group obtained 10 mg/day. The samples were excluded from the study if they resigned from the research, underwent severe side-effects or dismissed by the researchers for patients' own good, not consume the drugs for 2 (two) days in sequence, consumed sympathomimetic drugs, AH, systemic and local steroidal anti inflammatory, ketoconazole, erythromycin and cimetidine during the research, and not come to the medical control in the last evaluation on the fifteenth day.

The measurement of IL-4 level in nasal secretions was conducted by using nasal lavage. Each nasal cavity was inserted 5 ml of isotonic saline solution (it was warmed up in 37^0C) by using squirt 10 cc. The supernatant was collected and stored in a refrigerator in a temperature of -80^0C in Biomedical and Tissue Bank Unit Dr. Soetomo General Hospital Surabaya. The measurement and reading of IL-4 level in nasal secretion in the initial and last evaluation were conducted simultaneously. The statistical analysis on level of significance (p) of 0.05 or 5% applied 2 sample independent t-test to find out the comparison of desloratadine and loratadine therapy towards TNSS and IL-4 level in nasal secretions.

Results

Table 1. The severity scale of TNSS test

No	Symptom	Scale	Interpretation
1	Runny nose	0	no symptom
2	Stuffy nose	1 (mild)	symptoms that do not interfere
3	Sneezing	2 (moderate)	clear symptoms and signs, disturbing symptoms but still tolerable
4	Itchy	3 (severe)	symptoms and signs disturbed daily activities/sleep

Table 2. The comparison of reduced TNSS between Desloratadine group and Loratadine group

Reduced TNSS	Group		p
	Desloratadine	Loratadine	
N	12	12	
Average	7,67	2,25	0,000
SB	1,68	1,48	

Table 3. The comparison of reduced IL-4 level in nasal secretions between Desloratadine and Loratadine group

Reduced TNSS	Group		p
	Desloratadine	Loratadine	
N	12	12	
Average	7,67	2,25	0,000
SB	1,68	1,48	

There were 26 AR patients appointed as research samples. During the study, it was found 2 drop out cases which were 1 sample from study group on the fifteenth day and 1 sample from control group because the patient suffered from sore throat and had to consume other drugs. Therefore, the samples that can be analyzed were 24 patients. They were divided into two groups: 12 patients in study group and other 12 patients in control group. The male patients were 8 subjects while female patients were 16 subjects. The youngest age of those 2 groups was 21 years old while the oldest one in control group was 52 years old and in study group was 58 years old. The number of moderate-severe intermittent AR was 18 patients; mild intermittent AR was 3 patients; and mild persistent AR was 3 patients.

The result of statistical test using independent sample t-test was p=0.000 that indicated a significant different in the comparison of reduced TNSS between desloratadine and loratadine group (table 2). The result of statistical test using independent sample t-test was p=0.256 that indicated insignificant different (p>0.05) in the comparison of reduced IL-4 in nasal secretions between desloratadine and loratadine group (table 3). During the study, it was reported that the most frequent side-effect in both groups was sleepy which occurred in

3 patients (11.5%).

Discussion

The result showed that the average reduced TNSS in desloratadine group was 7.67 (SB 1.77) while in loratadine group was 2.42 (SB 1.62). The statistical test using independent sample t-test obtained the value of p=0.000. The value indicated a significant different in the comparison of reduced TNSS between desloratadine and loratadine group (p<0.05). It can be concluded that desloratadine was more effective compared to loratadine in reducing TNSS in AR patients. Desloratadine is the main active metabolite from loratadine. Seen from pharmacology, desloratadine and loratadine have similar pharmacokinetic profile which work in a quick phase and slow phase, inhibit the histamine bond with its receptor, inhibit infiltration and eosinophil activation to eliminate several mediators such as MBP, ECP, EPO, and EDN, inhibit mediator release from mast cell and basophile through direct obstacle in calcium ion canal to prevent further damage of the nasal mucosal epithelium. Based on the data of preclinical study, desloratadine was 60 times more selective towards H1 receptor than H2 receptor. Also, it had no affinity towards receptors of dopamine, monoamine oxidase, acetyl-cholinesterase, δ-amino butyric acid, and bradykinin [5]. In addition, loratadine is a selective tricyclic antihistamine towards peripheral H1 receptor and not indicate the activity towards H2 receptor

Based on preclinical study, the desloatadine affinity towards H1 receptor is 50-194 times higher than loratadine, cetirizine and feksonadine [12,13]. QingJia conducted a study on January until October 2014 in AR patients who underwent desloratadine and loratadine therapy. It revealed that desloratadine had the therapy effects such as runny nose, stuffy nose, itchy nose, sneezing and better edema inferior than loratadine [14]. The previous study had similarity with this study which is reduced TNSS in desloratadine is better than loratadine group.

The result of this study is not in accordance with the previous study. The double blind research in PAR patients who had allergic towards dermatophagoides farinea, cat's and dog's fur and obtained desloratadine 5 mg and levoceterizine 5 mg showed reduced IL-4 after 4 weeks therapy towards both drugs (18). Another study showed that the effect of desloratadine towards reduced IL-4 level in SAR patients after 2 weeks therapy with desloratadine 5 mg/day. A study in PAR patients also revealed that desloratadine reduced IL-4 in nasal rinses during four weeks of therapy [15].

The technique of nasal rinse collection in the previous study was conducted by provoking the previous allergen in order to determine the proper time to measure IL-4 level. The technique of nasal rinse collection in this study was not conducted. However, it was conducted in every patient with AR in order to recognize the difference of exposure time to allergens among the patients during sample collection. This condition can impact the measurement result of IL-4 level in various nasal secretions and we are not able to recognize the proper time to measure IL-4 level in nasal secretions [16].

The previous study indicated that IL-13 has a role in slow phase allergy in which an increase was obtained 24 hours after allergen provocation test [17]. IL-13 can affect chronic stuffy nose symptom in AR patients. Another study in AR patients obtained increased IL-4 and IL-13 level in nasal secretions after undergoing the provocation test of pollen and wheat powder allergen. The administration of anti IL-4 antibodies during the sensitization phase shows an inhibitory effect in the development of Th2. This suggests that IL-4 is important in fast type antigen responses. If IL-4 is given to animals that encounter sensitization, it is less affected in reducing the production of Th2 cytokines and eosinophil reflux. On the other hand, IL-13 has more roles than IL-4 after secondary antigen exposure [18]. The therapy implementation in allergic patients who has been given IL-4, IL-5 and IL-13 does not increase disease improvement and the symptoms caused by other mediators in allergic diseases [19].

The hypothesis of this study was not proven that desloratadine had bigger role in reducing IL-4 level in nasal secretions than loratadine in AR patients. It was because IL-4 is not the only factor affecting the occurrence of AR symptoms Several mediators and proinflammatory cytokines derived from mast cell degranulation play an important role in the emergence of clinical symptoms in AR. The previous research reported that there was no association between nose clinical symptoms with several signs of inflammation in perennial AR [20]. Other researches revealed that there was no significant association between the severity of nose symptoms and nose inflammation [21].

Conclusion

The present study can be concluded that desloratadine is more effective than loratadine in reducing TNSS; however, the effectiveness is similar in reducing IL-4 level in nasal secretions in AR patients. It is required to conduct allergen provocation test in order to determine the proper time to collect the samples to measure IL-4 level in nasal secretions. IL-4 has similar function to IL-13; therefore, it is required to conduct a research with IL-13 variable simultaneously. The result of desloratadine therapy which was significant in reducing TNSS can be considered as an alternative of AR therapy other than loratadine.

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