Effectiveness of Additional Intranasal Phototherapy through Decrease Score of Nose Symptom and Eosinophil Mucosa on Persistent Allergic Rhinitis

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Abstract

Background: Allergic rhinitis (AR) is a common atopic disease but the available treatment has limited used and success rate. It has been suggested that intranasal phototherapy represents an alternative choice in the treatment of AR.

Objective: This study aimed to analyze the effect of additional intranasal phototherapy to loratadine therapy compared with single loratadine therapy in order to decrease total nasal symptoms score (TNSS) and nasal mucosa eosinophil count in persistent AR patients.

Method: Fifty-four persistent AR patients were divided into two treatment groups: group A and B treated with 10 mg loratadine once a day with additional intranasal phototherapy at 660 nm. 4.4 minutes 3 times a day for group B. Evaluation was based on TNSS and nasal mucosa eosinophil countpre and post 14 days of treatment.

Result: The study conducted from July to August 2014 demonstrated significant average of TNSS decrease on group B compared to group A ($p = 0.002$). Also significant average of eosinophil mucosa nasal count decrease on group B compared to group A ($p = 0.049$). Both group A and B showed the smallest score of TNSS pre-therapy was 4 vs 6, however the highest score was 6 vs 12. Group A and B showed the smallest score of TNSS post-therapy was 0 vs 0, however the highest score was 8 vs 7.

Conclusion: Additional intranasal phototherapy to loratadine therapy showed more effective compared with single loratadine therapy in order to decrease TNSS and nasal mucosa eosinophil count in persistent AR patients.

***Keywords**: Allergic rhinitis, Eosinophil, Phototherapy intranasal, Loratadine.*

Introduction

Allergic rhinitis (AR) is the most common atopic disease that becoming global health problem. In persistent AR, the symptoms happen more than 4 weeks and characterized by the accumulation of inflammatory cells, especially eosinophils. Clinical evaluation and therapy of persistent AR can be performed subjectively by calculating the total nasal symptom score (TNSS) and objectively on nasal mucosal eosinophil[1]. Histamine interacts with H1 and H2 receptors increased permeability of blood vessels causes nasal congestion[2,3]. Histamine induces the expression of intracellular adhesion molecule-1 (ICAM-1) to help eosinophils migration to the nasal mucosa[4]. Eosinophils actively secrete chemical mediators and Reactive oxygen species (ROS) that worsen AR symptoms[5].

First-line therapy recommended Allergic rhinitis is loratadine, which can be administered singly or in combination with other anti-allergic drugs[6,7]. Loratadine inhibits eosinophils adhesion in the blood

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vessels and eosinophils accumulation in nasal mucosa. Significant decrease of eosinophils infiltration, the levels of eosinophil cationic protein (ECP), histamine and expression of ICAM-1 on RA patient's nasal rinse[8]. Therefore some experts develop new therapeutic modalities of intranasal phototherapy to optimalize AR therapy[1].

Intranasal phototherapy with visible red light inhibits inflammatory mediators release by eosinophils and stimulate nitric oxide (NO). Nitric oxide inhibits mast cell degranulation and cytokine expression. Increased vascular permeability as well as adhesion and leukocyte migration ultimately suppress the symptoms of AR. An intranasal phototherapy study with visible red light 660±5 nm wavelength showed improvement in AR clinical symptoms of 70%[9]. Intranasal phototherapy with a combination of UVA, UVB and visible light (mUV/vis) significantly decreased TNSS as well as the number inflammatory cells and mediators and were conducted with the aim of comparing the effectiveness of mUV/vis intranasal phototherapy with AH fexofenadine hydrochloride[1,2].

Separate research on the effectiveness of loratadine and intranasal phototherapy has been widely practiced abroad. Up to now, there has been no research on the effectiveness of intranasal phototherapy addition to loratadine therapy. Based on the above description the researchers aimed to determine the effect of intranasal phototherapy addition to loratadine therapy compared to single loratadine therapy in persistent AR patients which was assessed by TNSS and the number of nasal mucosal eosinophils.

Method

This study used a single-blind randomized controlled trial design with pre and post-test design which was held in January to November 2014 at the Outpatient Unit of Allergy Immunology Division and Clinical Pathology Installation of Dr.Soetomo Teaching Hospital, Surabaya. The samples were divided into 2 groups by block randomization with the number of 4 blocks to obtained 6 permutations. The control group (group B) received loratadine therapy and the study group (group A) received loratadine therapy combined with intranasal phototherapy. The study sample was mild to moderate-severe AR patients according to ARIA criterion 2008[6]. All samples underwent TNSS and nasal mucosa eosinophil pre- and post-therapy.

This study used consecutive sampling with inclusive and exclusive criteria. The inclusion criteria were having a pre-therapy GHT score ≥4, aged between 21 and 60 years, free anti-allergic drugs such as: AH (1 week), systemic corticosteroids (4 weeks), topical corticosteroids (2 weeks), topical decongestants (1 week), anticholinergic and chromoline (for 2 weeks), willing to take part in the research and signing the approval sheet to follow the research. The exclusion criteria were the presence of acute respiratory infections, acute and chronic paranasal sinusitis, medical rhinitis, nose abnormalities such as tumors, nasal polyp, severe deviation septum in conditions of pregnancy or lactation and having a history of loratadine allergy.

This research required 10 mg loratadine tablets and 8 units of intranasal phototherapy devices. Intranasal phototherapy equipment used was Bionase unit of Syrolight. Bionase unit consisted of control box size 23 x16 x 6 cm, 246 grams and 2 LED probes (Israel). The nasal mucosal eosinophil was applied to the glass object and then dried. Those preparations were stained with Wright staining and then examined their eosinophils using Olympus microscope with 1000 magnification. The sample was not allowed to receive other treatments that could interfere with the results of the study for 14 days. Then TNSS and nasal mucosal eosinophil were assesed.

The data were tabulated and analysed statistically using SPSS (SPSS. Inc. Chicago, IL) with significance level (p) of 0.05 or 5%. Analysis of age distribution, TNSS, and number of nasal mucosal eosinophils were obtained with Mann-Whitney U test. Sex distribution was analysed using Chi square test and side effects was with Fisher's exact test. The Wilcoxon signed rank test was used to determine the ratio of TNSS and the number of nasal mucosal post eosinophils in each group. Independent sample t-test was used to determine the percentage of TNSS decline and number of nasal mucosal post eosinophils between the two groups.

Results

TNSS score and Therapy

Group A had the smallest TNSS pre-therapy of 4 and the highest score of 11 (1 patient each, 3.7%). Group B had the smallest TNSS pre-therapyof 6 (3 patients, 11.1%) and the highest score of 12 (2 patients, 2.4%). Group A had the lowest TNSS post-therapy of 0 (3 patients, 11.1%) and group B had the lowest TNSS post-

therapy of 0 (1 patient, 3.7%). Group A had the highest TNSS post-therapy of 8 (1 patient, 3.7%) while group B was 6 patients (3.7%). The averageTNSS pre-therapy in group A was 7.67 (1.73) and group B was 9.41 (1.80). The average TNSS post-therapy in group A was 3.63 (2.08) and group B was 78 (1.40, Table 1.).

The average percentage of TNSS decrease post-therapy in group A was 55.2% while group B was 70.9%. The Independent sample t-test showed that the percentage between group A and B was significantly different (p = 0.002, Table 2).

Nasal Mucosa Eosinophil and Therapy

Groups A and B had the most eosinophils pre-therapy in the range of ≥10% to <25%. respectively. Group A had the least eosinophils pre-therapy in the range of ≥25% to <50% while group B was <10%. The average eosinophil pre-therapy in group A was 21.44 (19.14) and B was 32.93 (26.46).

Group A had the most eosinophils post-therapy of <10% and ≥10% to <25%. Group B had the most eosinophils post therapy of <10%. Group A had the least eosinophils post therapy of ≥50% while group B was ≥25% - <50% and ≥50%. The average eosinophils post-therapy in group A was 12.48 (14.93) and group B was 8.78 (12.75, Table 3.)

The average percentage of nasal mucosa eosinophil decrease in group A was 22.6% and group B was 64.5%. The independent sample t-test showed that the percentage decrease of nasal mucosal eosinophils between group A and group B was significantly different (p = 0.049, Table 4.)

Side Effect

The most common side effects reported by patients in groups A and B were drowsy. Dry mouth or throat in both groups happened in 1 patient (3.7%). The Fisher's exact test suggested that the distribution of side effect between the two groups was not significantly different (p = 1.000, Table 5).

Table 1. Total Nasal Symptoms Score Pre and Post Therapy

TNSS	Pre-Therapy (%)		Post-Therapy (%)	
	Group A	Group B	Group A	Group B
0	0 (0.0)	0 (0.0)	3 (11.1)	1 (3.7)
1	0 (0.0)	0 (0.0)	0 (0.0)	4 (14.8)
2	0 (0.0)	0 (0.0)	5 (18.5)	7 (25.9)
3	0 (0.0)	0 (0.0)	4 (14.8)	6 (22.2)
4	1 (3.7)	0 (0.0)	8 (29.6)	7 (25.9)
5	1 (3.7)	0 (0.0)	2 (2.4)	1 (3.7)
6	5 (18.5)	3 (11.1)	2 (2.4)	1 (3.7)
7	6 (22.2)	1 (3.7)	2 (2.4)	0 (0.0)
8	7 (25.9)	5 (18.5)	1 (3.7)	0 (0.0)
9	1 (3.7)	2 (7.4)	0 (0.0)	0 (0.0)
10	5 (18.5)	7 (25.9)	0 (0.0)	0 (0.0)
11	1 (3.7)	7 (25.9)	0 (0.0)	0 (0.0)
12	0 (0.0)	2 (7.4)	0 (0.0)	0 (0.0)
Average (SD)	7.67 (1.73)	9.41 (1.80)	3.63 (2.08)	2.78 (1.40)
Total (%)	27 (100)	27 (100)	27 (100)	27 (100)

Table 2. Average Percentage of Total Nasal Symptoms Score Decrease Pre and Post-therapy

TNSS Decrease	Group A	Group B
N	27	27
Average (%)	55.2	70.9
Standard Deviation (%)	21.6	12.7
Sig. (2-tailed)	0.002	

Table 3. Total Nasal Symptoms Score Pre and Post-therapy

Eosinophil (%)	**Pre-therapy**		**Post-therapy**	
	Group A	**Group B**	**Group A**	**Group B**
<10	5 (18.5)	3 (11.1)	11 (40.7)	17 (63)
≥10–<25	15 (55.6)	11 (40.7)	11 (40.7)	8 (29.6)
≥ 25–<50	3 (11.1)	6 (22.2)	4 (14.8)	1 (3.7)
≥50	4 (14.8)	7 (25.9)	1 (3.7)	1 (3.7)
Total	27	100	27	100

Table 4. Average Percentage of Nasal Mucosa Eosinophil Decrease

Eosinophil Decrease	**Group A**	**Group B**
N	24	25
Average (%)	22.6	64.5
Standard Deviation (%)	88.4	52.5
Sig. (2-tailed)	0.049	

Table 5. Side Effect

Side Effect	**Group A** **N (%)**	**Group B** **N (%)**	**Total (%)**	**P**
Drowsy	5 (18.5)	5 (18.5)	10 (18.5)	1.000
Dry Nasal	0 (0.0%)	1 (3.7)	1(1.9)	
Dry Mouth/throat	1 (3.7)	1 (3.7)	2(3.7)	
Dizzy	1 (3.7)	0 (0.0)	1(1.9)	
No symptom	20 (74.1)	20 (74.1)	40 (74.1)	
Total (%)	27 (100)	27 (100)	54 (100)	

Discussion

The results showed significant improvement of nasal congestionand rhinorrhea 80% and 81% (study group) and 31% and 14% (control group) respectively. A study investigated the effects of mUV/visintranasal phototherapy versus topical azelastine therapy in moderate persistent AR[7]. The average variation of TNSS pre and post-therapy might be due to the different sample criteria selected. This leads to differences in average TNSS pre-therapy as well as the possibility of decreasing TNSS as being summarized as average TNSS post-therapy. Another study using Bionase phototherapy tool compared 660 nm visible red light effect (study group) and sham illumination (control group)[9]. A similar study reported a decrease of all AR symptoms post 660 nm visible red light phototherapy[13]. Other studies showed a decrease in TNSS after intranasal phototherapy of visible red light for 14 days[14].

Other studies used different light showing a significant improvement in TNSS post-mUV/vis phototherapy of 50% in 11 patients (61.1%). The Hex fexofenadine group showed no significant improvement with 50% TNSS improvement in 2 patients (15.4%)[2]. This study used the Bionase intranasal phototherapy apparatus with LLLT technique did not cause any harmful side effects or interactions with[9]. Bionase efficiency as AR therapy occured because of its role in producing NO[15]. In this study the number of nasal mucosal eosinophil that could be analyzed was 24 of 27 patients in group A and 25 of 27 patients in group B. Three preparations of group A and two preparations of group B were not included in the statistical analysis.

Missing 5 samples happened because it had a pre value of 0 therefore in statistical analysis the result was not defined. Other descriptive research data on average percentage of nasal mucosal eosinophil pre- and post-loratadine with and without visible red light phototherapy were not found. The average percentage of nasal mucosal eosinophil decrease between the two groups was significantly different ($p = 0.049$). The average of nasal mucosal eosinophil decrease in group A was 22.63% smaller than the decrease in group B that was 64.46% although sample size for percentage analysis was below the minimum but with significant analysis results, the lack of eosinophil samples did not become obstacles and the results of the analysis were still acceptable.

A study showed similar results in decreasing the inflammatory cells (eosinophils, macrophages, neutrophils, lymphocytes) post-visible red light[11]. Previous studies showed a significant decrease of eosinophils, ECP and IL-5 post- mUV/vis intranasal phototherapy and visible red light[1]. Other studies showed a significant decrease in eosinophils, inflammatory cells, ECP, histamine and ICAM-1 expression after loratadine therapy[8]. Eosinophils reached nasal secretions in nasal cavity within 1 - 3 hours and stayed up to 3 days[16]. In this study Bionase phototherapy worked by producing NO which would inhibit eosinophil cell adhesion[17]. NO also played a direct role in modulation of immune response by influencing expression of adhesion molecule VCAM-1, ICAM-1 and endothelial E-selectin that were important for eosinophil adhesion[18].

Visible red light phototherapy with LLLT technique significantly interfered major transcription factors activity that governed IL-4 expression, IL-5 and eotaxin thus it could inhibited IgE production and eosinophil recruitment[19]. Research conducted on mice's BALF showed decreased infiltration of inflammatory cells (eosinophils, macrophages, neutrophils, lymphocytes), IL-4, IgE secretion and increased IFN-γ after phototherapy. The effects of phototherapy were reported having no side effects[20]. Side effects between two groups were not significantly different. Another study obtained dry nose, mouth and throat complaints post-loratadine in 23% of patients[21].

Conclusion

The addition of intranasal phototherapy to loratadine therapy compared to loratadine therapy singly was more effective in reducing TNSS and the number of nasal mucosal eosinophils of AR patients.

Ethical Clearance: The study protocol has been approved by the Medical Research Ethics Commission of Dr. Soetomo Teaching Hospital.

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Conflict of Interest: There is no conflict of interest.

References

1. Koreck AI, Csoma Z, Bodai L, Ignacz F, Kenderessy AS, Kadocsa E, et al. Rhinophototherapy: A new therapeutic tool for the management of allergic

rhinitis. J Allergy Clin Immunol. 2005;115(3):541–547.

2. Garaczi Supervisor E, Kemény L, Zs B. Histamin in allergic diseases:an old molecule in new concepts. Vol. 16, J. Photochem. Photobiol. B:Biol. 2004.
3. Pawankar R, Mori S, Ozu C, Kimura S. Overview on the pathomechanisms of allergic rhinitis. Asia Pac Allergy. 2011;1(3):157.
4. Sin B, Togias A. Pathophysiology of Allergic and Nonallergic Rhinitis. Proc Am Thorac Soc [Internet]. 2011;8(1):106–114.
5. Mandhane SN, Shah JH, Thennati R. Allergic rhinitis: An update on disease, present treatments and future prospects. Vol. 11, International Immunopharmacology. 2011. p. 1646–1662.
6. Bouquet J, Khaltaev N, Cruz A, Denburg J, Fokkens W, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). 2008;8–160.
7. Albu S, Baschir S. Intranasal phototherapy versus azelastine in the treatment of seasonal allergic rhinitis. Auris Nasus Larynx. 2013 Oct;40(5):447–451.
8. Ciprandi G, Pronzato C, Ricca V, Passalacqua G, Danzig M, Canonica GW. Loratadine treatment of rhinitis due to pollen allergy reduces epithelial ICAM-1 expression. Clin Exp Allergy [Internet]. 1997;27(10):1175–83.
9. Neuman I, Finkelstein Y. Narrow-band red light phototherapy in perennial allergic rhinitis and nasal polyposis. Ann Allergy, Asthma Immunol. 1997;78(4):399–406.
10. De Martinis M, Sirufo MM, Ginaldi L. Allergy and aging: An Old/new emerging health issue. Vol. 8, Aging and Disease. International Society on Aging and Disease; 2017. p. 162–75.
11. Wang D-Y. Risk factors of allergic rhinitis: genetic or environmental? Ther Clin Risk Manag. 2005;1(2):115–123.
12. Khan M, Khan MA, Shabbir F, Rajput TA. Association of Allergic Rhinitis with Gender and Asthma. 2013;120–122.
13. Hu K-H, Li W-T. Phototherapy for the Treatment of Allergic Rhinitis. In: Allergic Rhinitis. InTech; 2012.
14. Cingi C, Cakli H, Yaz A, Songu M, Bal C. Phototherapy for allergic rhinitis: A prospective, randomized, single-blind, placebo-controlled study. Ther Adv Respir Dis. 2010;4(4):209–213.
15. Zhang LM, Wang HL, Zhao N, Chen HX, Li YF, Zhang YZ. Involvement of nitric oxide (NO) signaling pathway in the antidepressant action of the total flavonoids extracted from Xiaobuxin-Tang. Neurosci Lett. 2014 Jul 11;575:31–36.
16. Watanabe K, Inoue S, Misu T, Edamatsu H. Cytolysis of eosinophils in nasal secretions. Ann Otol Rhinol Laryngol. 2003 Feb 1;112(2):169–173.
17. Chigaev A, Smagley Y, Sklar LA. Nitric oxide/cGMP pathway signaling actively down-regulates α 4β 1-integrin affinity: An unexpected mechanism for inducing cell de-adhesion. BMC Immunol. 2011 May 17;12.
18. Chuang YC, Chuang HY, Lin TK, Chang CC, Lu CH, Chang WN, et al. Effects of long-term antiepileptic drug monotherapy on vascular risk factors and atherosclerosis. Epilepsia. 2012 Jan;53(1):120–128.
19. Silva VR, Marcondes P, Silva M, Villaverde AB, Castro-Faria-Neto HC, Vieira RP, et al. Low-level laser therapy inhibits bronchoconstriction, Th2 inflammation and airway remodeling in allergic asthma. Respir Physiol Neurobiol. 2014 Apr 1;194(1):37–48.
20. Wang XY, Ma WJ, Liu CS, Li YX. Effect of low-level laser therapy on allergic asthma in rats. Lasers Med Sci. 2014;29(3):1043–1050.
21. Meltzer EO, Baena-Cagnani CE, Gates D, Teper A. Relieving nasal congestion in children with seasonal and perennial allergic rhinitis: Efficacy and safety studies of mometasone furoate nasal spray. World Allergy Organ J. 2013;6(1).