

Research Note

A Comparative Pilot Study of Symptom Improvement Before and After Phototherapy in Korean Patients with Perennial Allergic Rhinitis

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ABSTRACT

Although allergic rhinitis is not life threatening, it significantly influences the quality of a patient's life. This study is intended to evaluate the safety and efficacy of phototherapy with low-level energy of a 650 nm laser irradiation system in perennial allergic rhinitis patients. This clinical trial was an open-label, single-center study with 42 perennial allergic rhinitis subjects. Following laser irradiation in the nasal cavity with a laser irradiation system, the efficacy at weeks 1 through 4 was determined. The symptoms were scored with four parameters (nasal obstruction, rhinorrhea, sneezing and itching) before and after illumination of the laser, and the total score was recorded. A survey of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was conducted by patients before and after treatment. Following treatment, significant improvement in the clinical symptoms of nasal obstruction ($P < 0.001$), rhinorrhea ($P = 0.005$), sneezing ($P = 0.001$) and itching ($P = 0.003$) was reported by 68% of perennial allergic rhinitis patients. The overall RQLQ scores significantly improved by 45% from the baseline with the treatment after 4 weeks. These results indicate that phototherapy is an effective modality for treating perennial allergic rhinitis and is another option in the steroid-free management of immune-mediated mucosal diseases.

INTRODUCTION

Allergic rhinitis is one of the most common health problems among all the IgE-mediated allergic diseases (1). The characteristic symptoms of allergic rhinitis are rhinorrhea, nasal congestion, sneezing and nasal itching. Besides the nasal symptoms, non-nasal symptoms such as tears, ocular hyperaemia, itching around the eyes, itchy palate, etc. may also appear. Although such symptoms are usually considered nonserious, they do affect the social and daily activities of an individual, so that they sometimes have significant effects on the quality of life and even require considerable medical expenses (2–4).

Quite a number of allergic rhinitis patients have failed to achieve satisfactory improvement of symptoms through medication, and pharmacotherapy can be excluded special populations including pregnant or breastfeeding women (5). For these reasons, studies are constantly under way to develop new treatment options for allergic rhinitis patients.

Allergic rhinitis is a type of inflammatory response associated with a specific type of IgE-mediated inflammation of the nasal mucosa triggered by exposure to an allergen (6). In addition, it is often accompanied by other allergic diseases such as atopic dermatitis, and tends to show common pathophysiological features (7). As phototherapy has a strong immunosuppressive effect, treatments using ultraviolet (UV) and visible light have been used to cure various inflammatory skin diseases including atopic dermatitis (8–10). In addition, phototherapy causes apoptosis of T lymphocytes in skin diseases, reduces the number and function of dendritic cells and increases immunomodulatory cytokines, such as IL-10, and TGF- β (11–13).

Most previous studies (8,9,14,15) on phototherapy with a low-level energy for allergic rhinitis were limited to patients with seasonal allergic rhinitis, Caucasian patients and treatment with UV light. Thus, less reliable data are available from studies on patients with perennial allergic rhinitis and treatment with visible light, especially in the case of Asian patients. Furthermore, considering that phototherapy with UV light causes DNA damage, such therapy is mutagenic and carcinogenic (15–17). Therefore, this study was intended to clarify the safety and efficacy of phototherapy with low energy laser of a 650 nm in Korean patients with perennial allergic rhinitis.

MATERIALS AND METHODS

Subjects. This clinical study was conducted by complying with the relevant regulations such as the clinical study protocol approved by the IRB of Korea University Guro Hospital (IRB approval no., MD09022), the Declaration of Helsinki and the Good Clinical Practice. Hence, the objectives of the clinical study and the characteristics of the investigations performed were explained to the subject. The results obtained during the study period were recorded in case report form (CRF), and confidentiality was fully guaranteed. Facts on patient's indemnity were also explained to the subject. The clinical registry period was from 2010 to 2011 for 12 months. We excluded potential subjects from the study if they had

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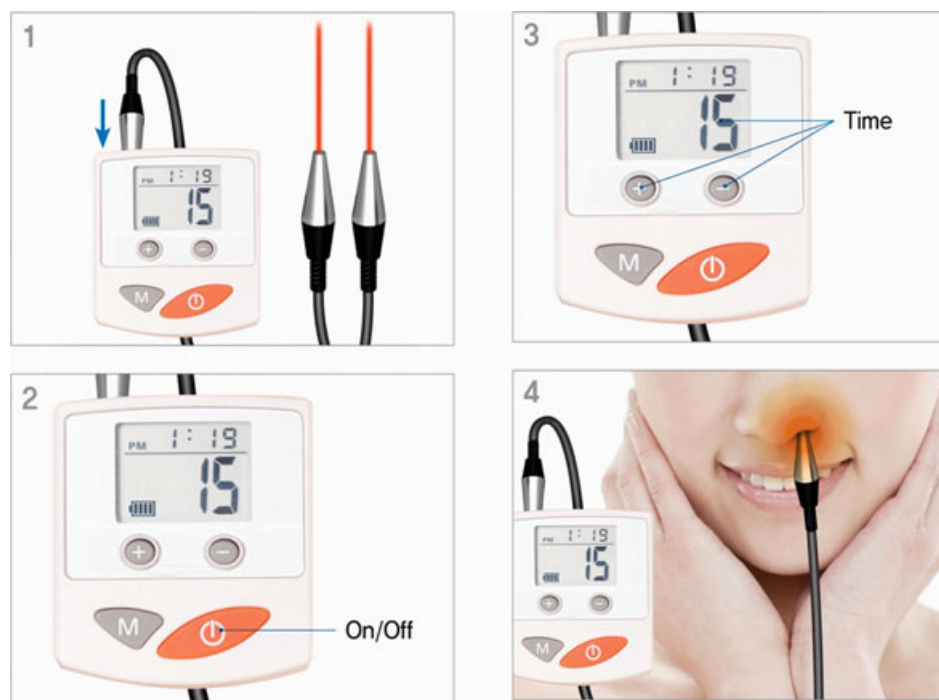


Figure 1. The procedure of the intranasal laser irradiation: (1) connect the irradiation part to the main body, (2) press On/Off button to switch on, (3) set the time by +/- buttons and (4) put irradiation part into the nostril.

undergone immunotherapy within 2 years, had asthma, upper or lower airways within 4 weeks of starting treatment, had serious systemic disease, were involved in another clinical study within 30 days before participating in this study had used any of the following drugs: topical corticosteroids within 2 weeks, systemic corticosteroids within 4 weeks, membrane stabilizers within 2 weeks, nasal decongestants within 3 days, antihistamines within 1 week and other than the above, if it was thought to be inappropriate to include a subject with clinical findings in this study according to the medical judgment of the principal investigator or subinvestigator.

Forty-two patients were enrolled, of which 28 were men (age, 42.64 ± 12.80 years) and 14 were women (age, 44.64 ± 9.69 years). All patients experienced symptoms on a daily basis despite with antihistamines and local treatment with steroid spray. The study overview was explained to the patients, and they were asked to sign the informed consent form. The eligibility criteria were as follows: a diagnosis of allergic rhinitis or a positive skin test using serology within 24 months before administration (Day 0) of an investigational product, narrow-band intranasal laser (Rhini Care[®]; SM Medical Co., Seoul, Korea) and a strong positive (+) response to house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) in skin prick test and the MAST (multiple allergen simultaneous test) during screening.

Diagnostic tests for allergic rhinitis. For skin testing, the method of prick testing was used. While 1% histamine solution was used as the positive control, saline solution was used as the negative control. The type(s) of antigen for testing was specified. A patient was judged to meet the inclusion criteria if they were diagnosed as having perennial allergic rhinitis by identification of the type(s) of antigen and grading on the basis of either the size of the wheal/erythema, or the A/H (allergen/histamine) ratio expressed as the ratio of the wheal/erythema reaction to the allergen to the wheal/erythema reaction to histamine.

After identifying the type(s) of antigen involved, regardless of determination techniques such as the radioallergosorbent test, MAST or the immunocapsulated hydrophilic carrier polymer (ImmunoCAP), the cases diagnosed as perennial allergic rhinitis were determined to meet the pre-defined inclusion criteria.

Study design. Over 4 weeks, the subject was exposed to the narrow-band intranasal laser twice daily (morning and evening). The device was developed in collaboration with medical devices in clinical trial center, Korea University. 650 nm laser source (ChungWoo, Co., Seoul, Korea) was used. The procedure of irradiation was illustrated in Fig. 1. The irra-

Table 1. Device irradiation parameters.

Parameter [unit]	
Emitter type	InGaAlP LED
Beam delivery system	Hand-held probe
Operating mode	Continuous wave
Average radiant power [mW]	5 mW
Beam profile	Gaussian
Beam spot size at target [cm ²]	0.13 cm ²
Exposure duration [s]	40 s
Radiant energy [J]	0.195 J
Radiant exposure [J cm ⁻²]	1.5 J cm ⁻²

diation part was inserted into the main body. The power button was pressed to power on. The timer was set by +/- buttons. The irradiation tip was slightly put in the nostril. Each intranasal cavity was irradiated with a starting dose of 1.5 J cm^{-2} . Every third treatment day, the dose was increased by 0.25 J cm^{-2} . The maximum dose was 2.5 J cm^{-2} . The detailed irradiation parameters are shown in Table 1. The starting dosage of laser and dose increment were determined on the basis of data from a previous study (9). The study plan is summarized in Table 2. The demographic data (Table 3) consisted of patients' age, height, weight and body mass index with each gender. We measured and recorded the subject's blood pressure, pulse rate and body temperature after resting in the sitting position for 5 min. As there was no laboratory test parameter, we inquired about the pregnancy status for female subjects of childbearing age who had not undergone a sterilization procedure. We scored the symptoms by the four parameters (rhinorrhea, nasal obstruction, itching and sneezing) and recorded the total score which was classified into four stages from 0 to 3 points (the score of 0 means no reaction; 1, moderate reaction; 2, severe reaction and 3 is the most severe) with 4TSS (Total symptom score), and the sum of four symptom scores was calculated. We checked the results of allergy tests (skin test and/or MAST) and determined patient eligibility (subject selection according to inclusion/exclusion criteria). We explained how to fill out the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) to each subject visiting the site, and took back the completed questionnaires. The screening visit was per-

Table 2. Summary of the study plan.

	The period of treatment with the laser system				
	Screening	Day 0	Week 2	Week 4	Unscheduled visits
Informed consent	✓				
Demographics	✓				
Vital signs	✓	✓	✓	✓	✓
Medical history	✓				
Medication history	✓		✓	✓	
Physical examination	✓	✓	✓	✓	✓
Pregnancy check (inquiry)	✓	✓	✓	✓	
TSS assessment	✓	✓	✓	✓	✓
Subject selection according to inclusion/exclusion criteria	✓				
QoL questionnaire		✓	✓	✓	
Dispense the study device		✓			
Distribute/collect the subject diary		✓		✓	
Concomitant medication		✓	✓	✓	✓
Adverse events (AEs)			✓	✓	✓

mitted to be on the same day as the first treatment (Day 0) visit. The items were recorded in the distributed subject diary from the exposure start date of the study device (Day 0) to the last visit date, and was submitted to the investigator on the last visit date. In principle, immunotherapeutic drugs were contraindicated throughout the study. If required to concomitantly use any of the contraindicated drugs for medical treatment during the study, the subject was immediately expelled from the study. However, for any administered concomitant medications (including herbal medicine and vitamin complexes), their product names (brand name and ingredient name for monotherapy; brand name for combination therapy), daily dose, route, purpose and start/end dates of administration as well as any changes in dosage and administration were recorded in the CRF.

Statistical Analysis. In this study, good efficacy was considered as being achieved if there were any changes from the baseline and changes in 4TSS at Week 4 indicated at least 50% of improvement compared with the baseline score. All the statistical outcomes are expressed as mean $\pm$ standard deviation (SD) and percentage (%) as appropriate. To

find out the difference of symptom scores, we employed the Wilcoxon signed-rank test. Wilcoxon's rank-sum test was also used to check the changes between genders. In general, the seven symptom scores are known to be associated with one another. In this study, we measured the Spearman correlation coefficients among the changes in scores. The statistical analyses were performed by the SAS software (Version 9.2; SAS Institute, Inc., Cary, NC). A P -value < 0.05 was regarded as statistically significant.

RESULTS

4TSS assessment

The scores by the four symptoms (rhinorrhea, nasal obstruction, itching and sneezing) were classified into four stages from 0 to 3 points (the score of 0 means no reaction; 1, moderate reaction; 2, severe reaction and 3 is the most severe) depending on the severity of the symptom as assessed by the 4TSS, and the sum of the four symptom scores was calculated before and after treatment at week 4.

After laser irradiation, significant improvement of the clinical symptoms of nasal obstruction ($P < 0.001$), rhinorrhea ($P = 0.005$), sneezing ($P = 0.001$) and itching ($P = 0.003$) was reported by 68% of the perennial allergic rhinitis patients (Table 4). Scores of nasal obstruction were decreased by 36%. Rhinorrhea scores were decreased by 34%. Sneezing scores decreased by 33%. Itching scores decreased by 25%.

Rhinoconjunctivitis Quality of Life Questionnaire

RQLQ was categorized into seven areas: daily activities, sleeping state, nasal symptoms, systemic symptoms, vitality state, emotional state and ocular symptoms. Each area had three to five questions with a maximum of five answer choices each (scored from 1 to 5; the score of 1 means no reaction; 2, mild reaction; 3, moderate reaction; 4, severe reaction and 5, the most severe reaction). The overall RQLQ scores improved significantly (by 45%) from the baseline to 4 weeks after treatment (Table 5). There was relatively linear association among the changes in the seven areas of RQLQ (Table 6). Table 6 shows the linear associ-

Table 3. Patients' baseline characteristics and demographics.

Variable	All patients	Female	Male	P -value
N (%)	42	14 (33.33%)	28 (66.67%)	
Age	43.31 $\pm$ 11.77	44.64 $\pm$ 9.69	42.64 $\pm$ 12.80	0.650
Height	1.69 $\pm$ 0.09	1.59 $\pm$ 0.06	1.74 $\pm$ 0.04	<0.001
Weight	65.07 $\pm$ 10.18	52.93 $\pm$ 5.05	71.14 $\pm$ 5.50	<0.001
BMI	22.60 $\pm$ 0.36	20.99 $\pm$ 0.80	22.81 $\pm$ 0.37	<0.001

All data are expressed as mean $\pm$ standard deviation (SD). P -values were obtained from Wilcoxon's rank-sum test.

Table 4. Total symptom score results of patients with perennial allergic rhinitis.

Variable	All patients			Female			Male			P -value [†]
	Before	After	P -value*	Before	After	P -value*	Before	After	P -value*	
Nasal obstruction	3.29 $\pm$ 1.08	2.47 $\pm$ 0.90	<0.001	3.07 $\pm$ 1.33	2.36 $\pm$ 0.92	0.031	3.41 $\pm$ 0.93	2.53 $\pm$ 0.90	0.002	0.838
Rhinorrhea	3.24 $\pm$ 1.18	2.57 $\pm$ 1.07	0.005	3.43 $\pm$ 1.45	3.00 $\pm$ 1.41	0.125	3.15 $\pm$ 1.03	2.32 $\pm$ 0.75	0.053	0.789
Sneezing	3.22 $\pm$ 1.08	2.43 $\pm$ 1.01	0.001	3.57 $\pm$ 1.02	2.73 $\pm$ 1.35	0.047	3.04 $\pm$ 1.09	2.26 $\pm$ 0.73	0.026	0.670
Itching	2.41 $\pm$ 1.05	1.87 $\pm$ 1.01	0.003	2.71 $\pm$ 1.38	2.00 $\pm$ 1.18	0.078	2.26 $\pm$ 0.81	1.79 $\pm$ 0.92	0.039	0.631

All data are expressed as mean $\pm$ standard deviation (SD). * P -values were obtained from Wilcoxon's signed-rank test for checking the changes between before and after treatments. † P -values were obtained from Wilcoxon's rank-sum test for checking the difference in changes between genders.

Table 5. Rhinoconjunctivitis quality of life questionnaire results in perennial allergic rhinitis patients.

Variable	All patients				Female				Male			
	Before	After	Difference	P-value	Before	After	Difference	P-value	Before	After	Difference	P-value
Daily activities	9.27 ± 3.17	6.74 ± 3.23	2.39 ± 3.31	<0.001	10.71 ± 3.02	7.50 ± 3.87	3.08 ± 2.35	0.004	8.52 ± 3.03	6.26 ± 2.77	1.95 ± 3.79	0.029
Sleeping state	7.00 ± 3.22	5.83 ± 3.31	1.63 ± 3.36	0.010	6.79 ± 4.26	5.91 ± 3.67	1.55 ± 3.05	0.152	7.11 ± 2.61	5.79 ± 3.19	1.68 ± 3.61	0.053
Nasal symptoms	12.17 ± 3.15	9.33 ± 3.35	2.90 ± 3.35	<0.001	12.79 ± 3.64	10.09 ± 4.18	3.45 ± 3.64	0.022	11.85 ± 2.89	8.89 ± 2.89	2.58 ± 3.22	0.003
Systemic symptoms	16.02 ± 6.04	11.83 ± 6.13	4.20 ± 4.00	<0.001	18.36 ± 7.08	12.36 ± 6.42	6.36 ± 3.80	0.002	14.81 ± 5.15	11.53 ± 6.11	2.95 ± 3.64	0.002
Vitality state	10.02 ± 4.52	8.13 ± 4.13	2.43 ± 4.26	0.003	12.00 ± 5.51	8.82 ± 3.68	3.73 ± 4.78	0.031	9.00 ± 3.62	7.74 ± 4.41	1.68 ± 3.86	0.058
Emotional state	9.54 ± 4.58	7.63 ± 4.03	2.37 ± 3.13	<0.001	10.21 ± 5.78	8.09 ± 4.01	3.18 ± 4.05	0.031	9.19 ± 3.89	7.37 ± 4.13	1.89 ± 2.47	0.005
Ocular symptoms	9.66 ± 4.34	7.47 ± 3.53	2.70 ± 2.93	<0.001	11.36 ± 4.63	8.00 ± 3.77	3.64 ± 3.72	0.016	8.78 ± 3.98	7.16 ± 3.45	2.16 ± 2.29	0.001

All data are expressed as mean ± standard deviation (SD). Difference = Symptom before treatment-after treatment (after 4 weeks). P-values were obtained from Wilcoxon's signed-rank test for checking the changes before and after the treatment.

Table 6. Linear association among the changes in the seven symptom scores.

	Daily activities		Sleeping state	Nasal symptoms		Systemic symptoms	Vitality state		Emotional state		Ocular symptoms
	Before	After		Before	After		Before	After	Before	After	
Daily activities	–		0.840	0.746	0.700	–	0.517	0.560	0.473		
Sleeping state	<0.001		–	0.623	0.534	0.460	0.465	0.396			
Nasal symptoms	<0.001		<0.001	–	0.619	0.700	0.253	0.518			
Systemic symptoms	<0.001		0.002	<0.001	–	0.727	0.511	0.509			
Vitality state	0.004		0.011	<0.001	<0.001	–	0.437	0.556			
Emotional state	0.001		0.010	0.177	0.004	0.016	–	0.347			
Ocular symptoms	0.008		0.031	0.003	0.004	0.001	0.060	–			

The data listed are Spearman's correlation coefficients (upper triangle) between the changes in two symptom scores among the 7 scores and the corresponding P-values (lower triangle).

ation among the changes in the seven symptom scores obtained using Spearman's correlation analysis. Most pairs among the seven symptom scores show statistically meaningful associations and all are positively correlated. For example, sleeping state and systemic symptoms are significantly associated with each other ($r = 0.534$, $P = 0.002$), but emotional state and nasal symptoms are not correlated with each other ($r = 0.253$, $P = 0.177$). Figure 2(a) shows the relationship between the changes in each area of RQLQ. It indicates a higher correlation between the changes in sleeping state and daily activities, ($r = 0.840$, $P < 0.001$), changes in nasal symptoms and daily activities ($r = 0.746$, $P < 0.001$) and changes in vitality state and systemic symptoms ($r = 0.517$, $P = 0.004$). We have represented significant linear associations as simple linear regression models, such as $Y = 1.186 + 0.756 \times X$ in Fig. 2(b). It implies that when the change in daily activities increased by 1 unit, the change in nasal symptoms increased by 0.756 units on average.

Adverse events

Narrow-band 650 nm wave length intranasal laser therapy was well tolerated by patients. Possible adverse events were nasal septum perforation, nasal dryness, burning, epistaxis (nosebleed), inflammation or stinging. However, no AEs were found during the treatment period. Therefore, safety of intranasal therapy was demonstrated.

Nasal endoscopic assessment

After 4 weeks of treatment via narrow-band 650 nm wave length intranasal laser therapy, all subjects enrolled were observed by nasal endoscopy for objective assessment compared with patients' visual analog scale scores (Fig. 3). Before treatment, a patient was edematous congestion of the inferior turbinate (black arrows) and nasal discharge (white arrow) occurred continuously due to perennial allergic rhinitis, after 4 weeks treatment, the nasal mucosa appears normal.

DISCUSSION

Avoidance of allergens is practically difficult and symptom relief is often limited in perennial allergic rhinitis, despite the availability of a number of pharmacological options. Some Western researchers have been studied *via* laser treatment of seasonal allergic rhinitis (8,9,14,15,18). However, there are few studies for perennial allergic rhinitis with Asian subjects. In that sense, the results of this study was meaningful and encouraging.

Our data revealed that intranasal phototherapy with a narrow-band 650 nm laser significantly suppressed the clinical symptoms of a strong positive reaction in perennial allergic rhinitis related to house dust mites. Koreck *et al.* investigated the mechanism by which irradiation of the nasal mucosa was able to locally restrain IL-5 which is a cytokine that elevates the maturation, activation and prolonged survival of eosinophils, the main effector cells in allergic rhinitis (9). In addition, the phototherapy can block H1 receptors that reduce allergic inflammatory responses mediated by mast cells, basophils, epithelial cells, eosinophils and lymphocytes (19). Furthermore, Csoma *et al.* showed that xenon chloride ultraviolet B laser with medium doses of 308 nm improved the clinical symptom of allergic rhinitis (20). In a previous study, Garaczi *et al.* even insisted that intranasal phototherapy with a

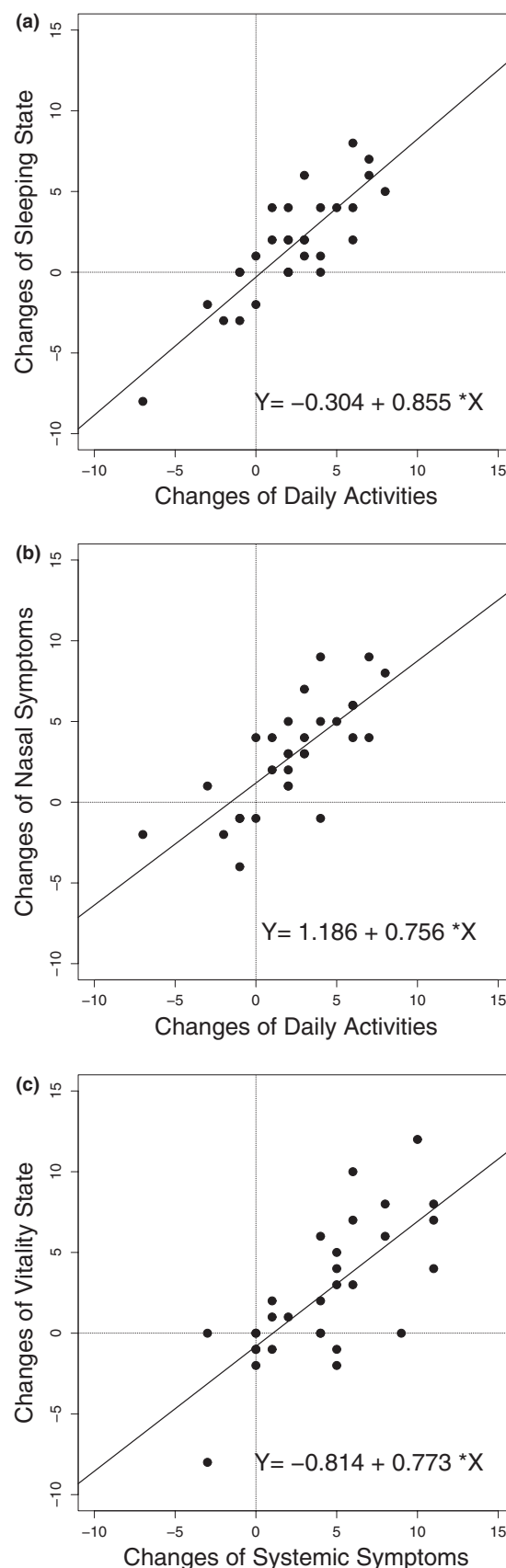


Figure 2. Scatter diagram illustrating subjects' changes in (a) daily activities with sleeping state, (b) daily activities with nasal symptoms and (c) systemic symptoms with vitality state.

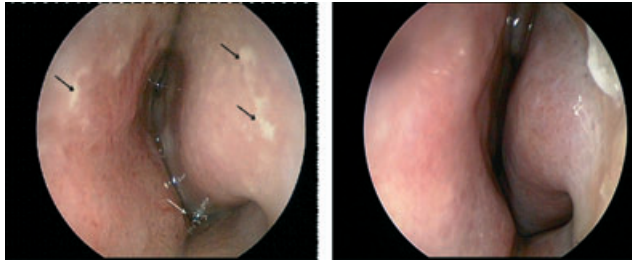


Figure 3. Typical endoscopic views of the nasal mucosa of a patient with allergic rhinitis: before (left) and after (right) treatment. Left: edematous congestion of the inferior turbinate and hyperemic mucosa (black arrows), and nasal discharge (white arrow).

combination of low-dose UVB, UVB and visible light for treatment of seasonal allergic rhinitis was significantly better than fexofenadine hydrochloride, a new generation antihistamine (18). However, dryness of the nasal mucosa occurred in many UV-treated patients as an adverse event. In our study, these adverse events were not reported due to only visible light (650 nm) was being used. The clinical scores for rhinorrhea, nasal obstruction, nasal itching and sneezing were reduced. Sneezing and nasal obstruction tended to improve from the second week, and rhinorrhea and nasal itching disappeared at the third week. The total nasal symptom score improved from the first week ($P < 0.001$). In the case of rhinorrhea, the score was not statistically different in females ($P = 0.125$), but slightly different in males ($P = 0.053$). Other variables were not different between genders (Table 4). After laser irradiation, the symptoms at week 4 compared with the baseline of the Rhinoconjunctivitis Quality of Life Questionnaire were significantly improved. Table 5 shows that, in particular, daily activities ($P < 0.001$), nasal symptoms ($P < 0.001$), systemic symptoms ($P < 0.001$), emotional state ($P < 0.001$) and ocular symptoms ($P < 0.001$) were significantly improved. On the other hand, the sleeping state was not still improved in the case of the females ($P = 0.152$) compared with the males ($P = 0.053$). We speculated that women are more sensitive than men. According to these results, we reconfirmed that allergic rhinitis, although not life threatening, significantly affects the quality of the patient's daily life such as their daily activities or their sleep.

Phototherapy with a low-level energy laser has been applied in many promising areas of basic research, and possible mechanisms of actions include increased respiration in mitochondria, activation of transcription factors, reduction in inflammatory mediators and oxidative stress and inhibition of apoptosis. Kreisler *et al.* showed that irradiation with low-level gallium-aluminum-arsenide (GaAlAs) laser resulted in human periodontal ligament fibroblast proliferation (21). Lim *et al.* illustrated that irradiation of human umbilical vein endothelial cells (HUVECs) with a 635 nm laser under hypoxic conditions reduced the intracellular reactive oxygen species production, leading to the elevation in vascular endothelial growth factor receptor-1 (VEGFR-1) levels and enhanced VEGF expression and extracellular signal-regulated kinase/mitogen-activated protein kinase activation (22). Houreld *et al.* showed that irradiation of diabetic wounded cells with a laser in the visible range (632.8 nm) was more beneficial than irradiation with a laser in the infrared range (23).

In addition, immunotherapy can be another treatment for allergic rhinitis. After successful specific immunotherapy, good correlation between skin prick test reaction and nasal symptoms

in allergic rhinitis patients was shown along with reduced immediate skin sensitivity. Immunotherapy, however, requires a high level of cooperation with patients for at least 3–5 years (24–26). Also, there are the risks of a serious adverse effect to specific immunotherapy, and fatalities have been reported (27,28).

Despite phototherapy with low-level energy being safe and well tolerated, some patients did not improve in our study. Endoscopic exam showed severe nasal septal deviation in two patients who did not respond. Three patients dropped out for personal reasons.

There are some limitations to this study. First, we could not design the “resting phase” for about 6 months and perform clinical trial evaluation to reconfirm the effects of laser irradiation. Second, a double-blinded and sham-controlled protocol was not employed in this study. This pilot study would require the inclusion of controls for further evaluation. Nevertheless, we checked all the enrolled subjects by performing a nasal endoscopy for objective assessment after 4 weeks to ensure that the possibility of a placebo effect was less. Unlike in the western countries, in Korea, dust mite antigens are the most frequent antigens for perennial allergic rhinitis (29). Therefore, dust mite antigens were chosen as the main antigens of inclusion.

In conclusion, our findings indicate that phototherapy with low-level energy represents an efficacious therapeutic modality for the treatment of perennial allergic rhinitis patients with symptoms not controlled by antihistamines.

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