Treatment of Postviral Olfactory Loss With Glucocorticoids, Ginkgo biloba, and Mometasone Nasal Spray

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Objective: To analyze the efficacy of treating postviral olfactory loss with glucocorticoids, Ginkgo biloba, and mometasone furoate nasal spray.

Design: Randomized trial.

Setting: Academic research.

Patients: Seventy-one patients who were diagnosed as having postviral olfactory loss.

Main Outcome Measures: All patients underwent olfactory function tests, including the butanol threshold test (BTT) and the cross-cultural smell identification test (CCSIT), and follow-up tests were performed 4 weeks later. In the interim, 28 patients were treated with prednisolone for 2 weeks (monotherapy), and the other 43 patients were treated with prednisolone for 2 weeks plus G. biloba for 4 weeks (combination therapy). All patients used mometasone nasal spray twice daily for 4 weeks.

Results: Scores on the BTT and CCSIT significantly increased after treatment in both groups (P < .001 for both).

The mean (SD) BTT score changes were 1.4 (2.2) in the monotherapy group and 2.2 (2.9) in the combination therapy group (P = .22). The mean (SD) CCSIT score changes were 0.9 (1.7) in the monotherapy group and 1.9 (2.7) in the combination therapy group (P = .11). On the BTT, the treatment response (defined as a score increase of ≥3) rates were 32% (9 of 28) in the monotherapy group and 37% (16 of 43) in the combination therapy group (P = .66), and the odds ratio was 1.25 (95% confidence interval, 0.46-3.42). On the CCSIT, the treatment response rates were 14% (4 of 28) in the monotherapy group and 33% (14 of 43) in the combination therapy group (P = .08), and the odds ratio was 2.89 (95% confidence interval, 0.84-9.97).

Conclusions: Olfactory function in patients with postviral olfactory loss was significantly improved by both treatment modalities. Although the treatment response was not statistically different between the monotherapy group and the combination therapy group, the addition of G. biloba showed a tendency of greater efficacy in the treatment of postviral olfactory loss.


Olfaction is an important sense in humans, although its significance is frequently ignored by lay people and by physicians. However, patients with olfactory loss seek to recover their olfaction. The 3 main causes of olfactory loss are head trauma, chronic sinonasal inflammation, and viral infection of the nose. Olfactory disorder is common, although its mechanism is not clearly understood. Therefore, treatment methods for olfactory loss are not well established.

In particular, postviral olfactory loss is a complicated disease. Upper respiratory tract viral infection is exceedingly common. The origins of upper respiratory tract infections include rhinovirus, influenza viruses, parainfluenza viruses, and respiratory syncytial virus. However, which viruses cause postviral olfactory loss is unknown, as well as who is susceptible to olfactory damage after the common cold. Furthermore, the role of the olfactory neural system in postviral olfactory loss is unknown. Therefore, these factors make treatment difficult. On the other hand, the constant regeneration of olfactory receptor neurons (the primary neurons in the olfactory nervous system) facilitates recovery of olfactory dysfunction. Although several researchers have tried to treat postviral olfactory disorder, more research is required relative to its mechanism as a peripheral neural degenerative disease. In this study, we treated patients with oral prednisolone or with a combination of oral prednisolone and G. biloba and analyzed the efficacy of the 2 regimens.
METHODS

PATIENTS

This study included 71 patients who visited the Chemosensory Outpatient Clinic of Seoul National University Bundang Hospital, Seongnam, Korea, from July 1, 2007, through June 30, 2008. All patients reported reduced subjective sense of smell after upper respiratory tract infection. Their mean age was 53.1 years (age range, 18-81 years), and 51 were female. Inclusion criteria were as follows: history of upper respiratory tract infection immediately before postviral olfactory loss, sudden onset of postviral olfactory loss, a visit within 12 months after onset of postviral olfactory loss, and no evidence of sinus inflammation on computed tomographic osteomeatal or panasal sinus views. Exclusion criteria were as follows: history of olfactory loss, history of head trauma, history of oral or nasal corticosteroid use, concurrent memory loss, presence of nasal discharge, allergic rhinitis, and chronic rhinosinusitis. This study was approved by the institutional review board of Seoul National University Bundang Hospital, Seoul, Korea.

OLFACTORY FUNCTION TESTS

At the first visit, all patients underwent olfactory function tests, including the butanol threshold test (BTT) and the cross-cultural smell identification test (CCSIT) (Sensomics, Inc, Haddon Heights, New Jersey), and follow-up tests were performed 4 weeks after the first evaluation of olfactory function. Odor threshold was determined using the BTT. The BTT composed a series of 13 concentrations of N-butanol (Sigma, St Louis, Missouri) in mineral oil (Sigma). Each threshold level was 3-fold serially diluted from 100% N-butanol (concentration level 0) to concentration level 12. The BTT was a 2-alternative forced-choice procedure. At each examination, 2 bottles were given to the examinees to squeeze and sniff. One bottle contained mineral oil, and the other bottle contained a given concentration of butanol. The examinees chose the bottle that they believed contained the odor. The examination was started at concentration level 12, and the odor threshold was defined as the concentration level at which the butanol bottle was correctly identified by the examinee in 5 consecutive trials. Odor identification was determined using the 12-item CCSIT. The BTT was performed in each nostril separately, but the CCSIT was performed in both nostrils simultaneously. For the CCSIT, the odor threshold of a patient was defined as the mean odor threshold of both nostrils. For the BTT, anosmia was defined as concentration levels 0 to 3, severe hyposmia as levels 4 to 5, moderate hyposmia as levels 6 to 8, mild hyposmia as levels 9 to 10, and normosmia as levels 11 to 12. For the classification of severity, odor threshold rather than odor identification was used because odor threshold is less confounded by several factors such as educational level, generation gap, regional variation, and sex difference. For the CCSIT, the same scoring system as for the BTT is applied for the classification of severity.

MEDICAL TREATMENT

At the first visit, patients were randomly assigned to 1 of 2 medication regimens. Twenty-eight patients were treated with oral prednisolone for 2 weeks (monotherapy), and the other 43 patients were treated with oral prednisolone for 2 weeks plus Ginkgo biloba (Ginexin; SK Pharmaceuticals, Suwon, Korea) for 4 weeks (combination therapy). The dosage of prednisolone was tapered over 2 weeks as follows: 30 mg/d for the first 3 days, 20 mg/d for 4 days, and 10 mg/d for 7 days. Eighty milligrams of G biloba was administered 3 times daily for 4 weeks. All patients were also instructed to administer 2 puffs of mometasone furoate nasal spray per nostril twice daily for 4 weeks.

STATISTICAL ANALYSIS

Differences in the BTT or CCSIT scores between study groups were analyzed using the Mann-Whitney test. Wilcoxon signed rank test was used to compare treatment results in each group. Categorical data were examined using the Pearson product moment correlation test for homogeneity. Correlation between the BTT and CCSIT was analyzed using the Spearman rank correlation test. P < .05 was considered statistically significant.

CHARACTERISTICS OF POSTVIRAL OLFACTORY LOSS

A higher incidence of postviral olfactory loss was noted in May and June, with the lowest incidence occurring during the winter months (Figure 1). The mean (SD) onset of postviral olfactory loss occurred 3.4 (3.5) months before the first visit (3.7 [2.5] months in the monotherapy group vs 3.2 [2.6] months in the combination therapy group [P = .42]). No statistically significant difference was noted in age between the 2 groups (Table). On the basis of the BTT results, 17 patients (24%) had anosmia, 25 patients (35%) had severe hyposmia, 23 patients (32%) had moderate hyposmia, 5 patients (7%) had mild hyposmia, and 1 patient (1%) had normosmia. There was no statistically significant difference in the severity of postviral olfactory loss between the 2 groups.

No statistically significant difference was found between the odor threshold of the right nostril and that of the left nostril (P = .40), showing that the severity of olfactory neural damage was similar on both sides. The BTT score was significantly correlated with the CCSIT score at the initial olfactory assessment (r = 0.459, P < .001) (Figure 2).

CHANGE IN OLFACTORY FUNCTION

On the BTT, the mean (SD) odor threshold was 4.8 (2.4) at the initial examination and significantly increased to
6.7 (2.8) after 4 weeks of treatment (P < .001) (Figure 3A). On the CCSIT, the mean (SD) odor identification was 3.8 (2.4) before treatment and significantly increased to 5.3 (2.7) after treatment (P < .001) (Figure 3B).

Change in olfactory function was analyzed by study group. The mean (SD) BTT score changes after treatment were 1.4 (2.2) in the monotherapy group and 2.2 (2.9) in the combination therapy group (P = .22). The mean (SD) CCSIT score changes after treatment were 0.9 (1.7) in the monotherapy group and 1.9 (2.7) in the combination therapy group (P = .11). Absolute change in the odor threshold and odor identification scores showed that study group did not affect treatment outcome.

Treatment outcome was evaluated from the standpoint of the treatment response rates. Treatment response was defined as an increase of 3 or higher in the odor threshold or odor identification scores. On the BTT, the treatment response rates were 32% (9 of 28) in the monotherapy group and 33% (14 of 43) in the combination therapy group (P = .08), and the odds ratio was 2.89 (95% confidence interval, 0.84-9.97) (Figure 4B).

**COMMENT**

Postviral olfactory loss occurs abruptly due to viral infection of the olfactory neural system in the nose. However, recognition is usually delayed several months after occurrence. With the common cold, patients usually experience transient olfactory and taste loss. Temporary chemosensory disorder in the common cold is mainly caused by mucosal swelling of the olfactory cleft, which results in conductive postviral olfactory loss. Patients generally expect that their olfactory dysfunction will recover, as it may have done in a previous common cold, which is why diagnosis is delayed. This study showed that the viral infections associated with sensorineural postviral olfactory loss primarily occurred during the spring and summer rather than the winter. The reason is unclear because the viral origin is undefined. However, specific causal viruses are presumed, as well as hosts who are more susceptible to postviral olfactory damage. This study also showed that the patients' first visit was about 3 months after a common cold. Such delay prevents early medical intervention for postviral olfactory loss. There has been no study to date about the effects of immediate treatment of postviral olfactory loss, although otolaryngologic treatment commences immediately after sudden sensorineural hearing loss or facial nerve paralysis, which are other cranial nerve diseases. The olfactory neural system is the only cranial neural system that regenerates throughout life, which may be why delayed recovery of olfaction is not uncommon. Our study revealed an association between medication use and recovery even if medication was administrated 3 months after viral infection. A previous study found a statistically significant correlation between the degree of improvement and the length of follow-up for patients with the common cold.

Glucocorticoid is a widely used drug for neuroinflammatory disease. However, the effectiveness of its immediate use is controversial even in sudden sensorineural hearing loss. Given that the administration of prednisolone was ineffective in the treatment of postviral olfactory loss, further studies are needed to determine the optimal treatment strategy for this condition.
alone to treat postviral olfactory loss was delayed herein by more than 3 months, its efficacy under these circumstances may be more controversial. Nevertheless, the powerful regenerative potential of olfactory neural cells may justify delayed medication use. In animal or in vitro models, glucocorticoid was effective in olfactory mucosal regeneration by increasing Na⁺/K⁺/H⁺ adenosine triphosphatase expression⁵ or by enhancing neural apoptosis.⁶ Ginkgo biloba was also effective in olfactory regeneration in an anosmic mouse model.⁷-⁹ Although studies¹⁰,¹¹ have demonstrated partial effectiveness of nasal glucocorticoid spray in improving olfactory loss associated with sinonasal inflammation, studies¹²,¹³ about its effectiveness in postviral olfactory loss are rare. While systemic glucocorticoid is the most popular medication for olfactory loss in humans, its effectiveness in postviral olfactory dysfunction is unclear.

In a large study¹⁴ of 262 patients who were examined using the “Sniffin’ Sticks” test kit, 31.7% of patients exhibited an increase in the threshold discrimination identification (TDI) score (odor threshold, odor discrimination, and odor identification [maximum score, 48 points]) of more than 6 points without any treatment. The authors regarded 12.5% (6 of 48 points) improvement in the TDI score as significant olfactory improvement. Lipoic acid was used in another study¹⁵ to treat postviral olfactory loss in 23 patients. It was effective in 35% of patients, whose TDI scores increased by more than 5.5 points. A long-term follow-up study³ of improvement in olfactory function after loss showed that 14 of 21 patients (67%) after a common cold improved their scores on the University of Pennsylvania Smell Identification Test (maximum score, 40 points) by 4 or more points (a 10% improvement). In another study,¹⁶ local corticosteroid injection was performed on the nasal mucosa near the olfactory cleft, and the improvement rate in olfactory loss due to upper respiratory tract infection was 49.6% immediately after treatment.

Our study revealed that the odor threshold and odor identification scores significantly improved after treatment in both study groups. A limitation is that this study lacked an untreated control group; therefore, significant improvement in the scores may not represent treatment effects. Furthermore, a test score improvement may not represent subjective improvement. For this reason, treatment response in this study was defined as a score increase of ≥3 or higher (a 25% improvement), which was considered a clinically significant improvement. There was no statistically significant difference in treatment response rates between the 2 study groups on the BTT or
This study showed that olfactory function significantly improved in patients with postviral olfactory loss after treatment with glucocorticoids, G biloba, and mometasone furoate nasal spray. Although combination therapy with oral prednisolone and G biloba did not show significantly better efficacy than monotherapy with oral prednisolone, G biloba might be helpful in improving odor identification. Many more patients experience postviral olfactory loss and seek recovery of their olfactory function than otolaryngologists have previously thought. Its pathogenesis is not well understood; therefore, treatment methods are undeveloped. Postviral olfactory loss is caused by neurodegeneration of cells in the olfactory neural system. More clinical trials are required to evaluate drugs shown to be effective against neurodegeneration for the future treatment of olfactory disorder.

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