

Efficacy of mometasone furoate nasal spray for nasal symptoms, quality of life, rhinitis-disturbed sleep, and nasal nitric oxide in patients with perennial allergic rhinitis

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ABSTRACT

Intranasal corticosteroid therapy has exhibited effectiveness for improving nasal symptoms and quality of life (QOL) scores associated with seasonal allergic rhinitis. We prospectively investigated the efficacy of mometasone furoate nasal spray (MFNS) for improving the total nasal symptom score, QOL score, and sleep quality in subjects with perennial allergic rhinitis (PAR). Nasal airway conditions were also objectively assessed by measuring nasal nitric oxide (NO). Fifty-seven patients with PAR were randomized to MFNS or placebo for a 14-day, double-blind, crossover study. The subjects recorded their symptoms on nasal symptom forms and a visual analog scale. QOL and sleep quality were surveyed in accordance with the Japanese version of the Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ) and the Japanese version of the Epworth Sleepiness Scale. Nasal NO was measured during a single exhalation using a chemiluminescence analyzer. MFNS treatment achieved significant reductions versus placebo for total nasal symptoms ($p = 0.001$). There were significant decreases of the usual daily activity domain ($p = 0.005$), outdoor activities ($p = 0.01$), social function ($p = 0.05$), and the overall QOL score ($p = 0.05$) of JRQLQ with MFNS therapy versus placebo. A significant reduction of the sleepiness scale was also observed in the MFNS group with high sleep disturbance ($p = 0.01$). A significant decrease of nasal NO was found in the MFNS group ($p = 0.01$), especially among patients with severe nasal symptoms ($p = 0.005$). This prospective study indicated that MFNS therapy significantly improves nasal symptoms, QOL, sleep quality, and upper airway condition in Japanese subjects with PAR.

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Allergic rhinitis (AR) is a common chronic inflammatory disease with an increasing prevalence worldwide that causes social and economic burdens. AR also has a significant impact on the quality of life (QOL) and on sleep. Our recent study showed that the prevalence of AR was 44.2% in 1540 subjects aged between 20 and 49 years, an increase of nearly 10% over the last 10 years.¹ Among the subjects, 20% had perennial AR (PAR) due to mites. Fifty-nine percent of all 1540 subjects were sensitized to mites (16% to mites only and 43% to cedar and mites).

Mast cell degranulation, release of inflammatory mediators, and infiltration of inflammatory cells occur within the nasal mucosa and conjunctival epithelium, resulting in nasal symptoms, such as sneezing, rhinorrhea, congestion, and nasal itching. Ocular symptoms (itching and watering of the eyes) also occur in up to 80% of persons with AR.

The pharmacologic management of AR includes H₁-antihistamines, antileukotrienes, and intranasal corticosteroids (INSs). INSs are recommended as first-line therapy, especially for patients with moderate-to-severe or perennial symptoms and when nasal obstruction is a major concern.² Recent once-daily INSs are topically effective synthetic glucocorticoids with a high affinity for the glucocorticoid receptor and minimal adverse effects because of their low bioavailability.³ It has been confirmed by meta-analysis that the efficacy of INS is greater than that of second-generation antihistamines.⁴

Patients express preferences when given the chance to compare various attributes of INS that influence willingness to continue therapy.⁵ In particular, subjective assessment of the smell, taste, aftertaste, throat rundown, nose run-out, and feel of sprays in the nose and throat seems to be quite different between Asians

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Table 1 Demographics in the double-blind, placebo-controlled, crossover trial

Age Group	No. (%)	Male/Female	TNSS (baseline)	
17–19 yr	13 (23)	3/10	4.54	0.57
20–29 yr	41 (73)	27/14	3.88	0.26
30–45 yr	2 (4)	2/0	4.00	1.00
22.7 ± 3.8	56	32/24	4.05	0.23

TNSS total nasal symptom score.

(including Japanese) and westerners. At present, INSs are not widely used in Asian countries for the following reasons: (1) patients do not like the smell or feel of INS, (2) patients do not like putting something into the nose, and (3) physicians and patients do not understand that the efficacy of INS is enhanced by continuous use. In addition, the primary reason is that no appropriate study about randomized, double-blind, placebo-controlled trials of INSs in Asians have been found in Pubmed.

Mometasone furoate nasal spray (MFNS) is a once-daily INS with proven efficacy for providing clinically significant relief of nasal symptoms in western subjects with seasonal AR (SAR).^{6,7} The present trial was a randomized, double-blind, placebo-controlled, crossover, parallel-group study of MFNS in PAR patients. The efficacy of MFNS for nasal symptoms, QOL, and sleep disturbance was evaluated by using the nasal symptom score, visual analog scale, the Japanese version of the Rhinoconjunctivitis Quality-of-Life Questionnaire (JRQLQ), and the Japanese version of the Epworth Sleepiness Scale (JESS). In addition, the usefulness of MFNS for PAR was objectively evaluated by investigating the changes of nasal nitric oxide (NO).

PARTICIPANTS AND METHODS

Participants

Thirty-three men and 24 women aged from 17 to 43 years (mean, 22.6 years) were recruited for this study from the general public through the Division of Otorhinolaryngology Head and Neck Surgery of the University of Fukui. All participants were Japanese. The inclusion criteria were a presence of moderate or severe nasal symptoms for 1 week before starting the crossover trial (total nasal symptom score [TNSS], ≥ 3 points), detection of *Dermatophagoides pteronyssinus*- or *Dermatophagoides farinae*-specific IgE in the blood, a positive nasal challenge test with a house-dust-coated disk, and residence in Fukui. Demographics with baseline is listed in Table 1. The study was approved by the Ethics Committee of the University of Fukui. The exclusion criteria were as follows: infections or systemic

mycoses, untreated infections, or herpes simplex of the eye; recurrent epistaxis; women who were pregnant, possibly pregnant, or lactating; nasal complications; acute upper respiratory tract inflammation; and patients receiving mite-specific immunotherapy. This trial was started in November 2009. It was confirmed by Durham's technique that pollen was not in the atmosphere around Fukui University Hospital during the study period.

Study Design

This was a single-center, randomized, double-blind, placebo-controlled, crossover trial. MFNS was administered as 2 puffs (100 µg each) into each nostril once daily for 14 days. The placebo was also given by the same method as MFNS for 14 days (Fig. 1). Twenty-nine and 28 subjects were assigned to groups A and B, respectively. The investigator assessed the eligibility of the subjects and gave them adequate information about the trial by using the patient information/consent form. Use of inhibitors of chemical mediator release, antihistamines, steroids, vasoconstrictors, anticholinergics, histamine-containing -globulin preparations, or herbal medicines prescribed for rhinitis or the common cold was prohibited during the study period. MFNS was purchased from MSD Co., Ltd. (Tokyo, Japan). The placebo was prepared in the same container as that used for MFNS at the Department of Pharmacy, Faculty of Medical Service, University of Fukui. All participants recorded the diary every day, when MFNS/placebo was used.

Recording and Assessing Symptoms and QOL

The subjects recorded the number of sneezing episodes and number of times that they needed to blow their noses daily on nasal symptom forms. Using this information, the patients were graded on a scale of 0–4 (0 none, 1 1–5 times, 2 6–10 times, 3 11–20 times, and 4 ≥ 20 times). Nasal congestion, nasal itching, eye itching, and watering of the eyes were recorded on a scale of 0–3 (0 no symptoms, 1 mild symptoms, 2 moderate symptoms, and 3 severe symptoms).^{8,9} The total daily symptom score was calculated, and the average daily scores for 1 and 2 weeks were used for analysis.¹⁰

QOL was surveyed by using the JRQLQ on days 0 and 14.¹¹ The severity of sleep disturbance was investigated by using the JESS on days 0 and 14.¹²

Measurement of Nasal NO

Nasal fractional exhaled NO (FENO) was measured during a single exhalation by using a chemiluminescence analyzer (NOA 280; Sievers, Boulder Co). After inhaling ambient air, the subjects expired through a nasal olive placed into the nostril against positive pressure, aiming to achieve a flow rate of 50 mL/s under

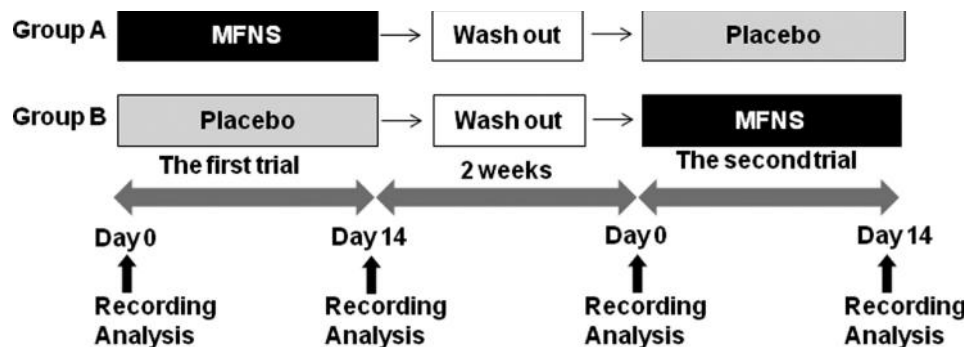


Figure 1. Diagram of the present single-center, randomized, double-blind, placebo-controlled, crossover study. Subjects were randomized into two groups (group A, $n = 29$; group B, $n = 28$) and mometasone furoate nasal spray (MFNS) or placebo was given as 2 puffs once daily for 14 days. Japanese version of the Rhinoconjunctivitis Quality of Life Questionnaire, Japanese version of the Epworth Sleepiness Scale, and nasal nitric oxide (NO) were recorded and analyzed on the days indicated with arrows.

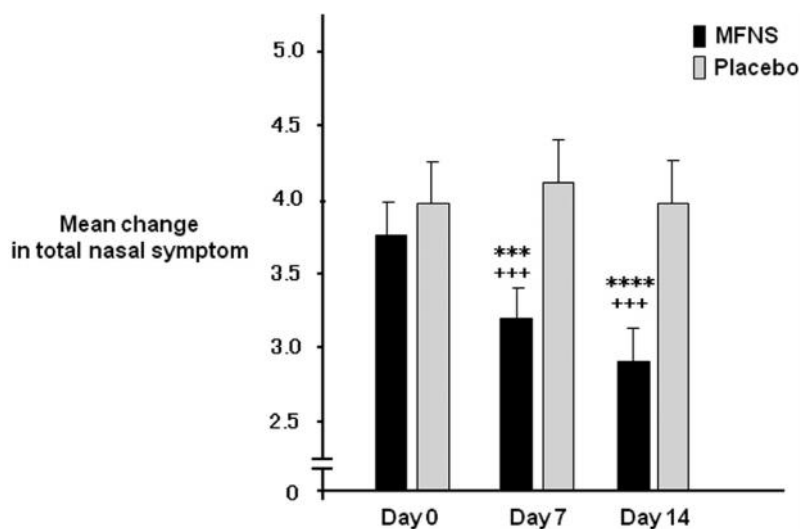


Figure 2. Mean total nasal symptom scores. A significant decrease of the total nasal symptom score was seen in the mometasone furoate nasal spray (MFNS) group (** $p = 0.001$ and **** $p = 0.0001$, versus day 0). $p = 0.001$ (versus placebo).

visual control on a computer screen. Oral FENO was also measured by the method recommended by the American Thoracic Society,¹³ except for the mouth-piece. Measurements were performed at least in triplicate and the mean of three reproducible values was calculated for analysis. Acceptable measurements showed a clearly identifiable plateau within 10% for each measurement (typically 5%) and a flow rate within 10% (typically 5%) of the target rate during plateau measurement. Nasal FENO was adjusted by subtracting oral FENO to calculate nasal NO (nasal NO = nasal FENO - oral FENO).

Statistical Methods

Data were expressed as the mean ± standard error. Statistical analysis was performed by using the Wilcoxon signed-ranks test to assess the significance of differences. When we observed the effect on the sleepiness scale or the effect on nasal NO, the subjects were segregated into two groups by severity. The segregation was performed using a *post hoc* analysis.

RESULTS

Symptom Score

One of the 57 subjects discontinued the trial because influenza occurred during the study period. Recorded diaries proved that compliance in the active drug group and the placebo group was 96.8 and 97.2%, respectively.

The TNSS was calculated and compared between before and after administration of MFNS or placebo. In the MFNS group, TNSS showed a significant decrease on day 7 and was decreased further on day 14 (mean standard error: 3.75 ± 0.24 on day 0 versus 3.12 ± 0.21 on day 7 [$p = 0.001$] versus 2.79 ± 0.21 on day 14 [$p = 0.0001$]; Fig. 2). There was no difference between the MFNS and placebo groups on day 0, but the score was significantly lower on days 7 and 14 in the MFNS group ($p = 0.001$).

With respect to efficacy for individual symptoms, administration of MFNS for 2 weeks reduced the scores for rhinorrhea ($p = 0.001$), sneezing ($p = 0.001$), congestion ($p = 0.001$), and nasal itching ($p = 0.05$) in

Table 2 Symptom scores (all subjects)

	MFNS				Placebo			
	Day 0		Day 14		Day 0		Day 14	
Rhinorrhea	2.10	0.13	1.36	0.12***	2.14	0.12	2.12	0.13
Sneezing	1.74	0.14	1.26	0.10***	1.69	0.13	1.74	0.13
Congestion	2.07	0.13	1.45	0.13***	2.03	0.13	1.93	0.15
Nasal itching	1.14	0.14	0.81	0.13*	1.00	0.14	0.84	0.12
Eye itching	0.84	0.14	0.74	0.12	0.97	0.12	0.88	0.12
Watering of the eyes	0.60	0.12	0.34	0.10*	0.50	0.10	0.45	0.10

Mean standard error.

* $p < 0.05$ compared with day 0; *** $p < 0.001$ compared with day 0.

MFNS mometasone furoate nasal spray.

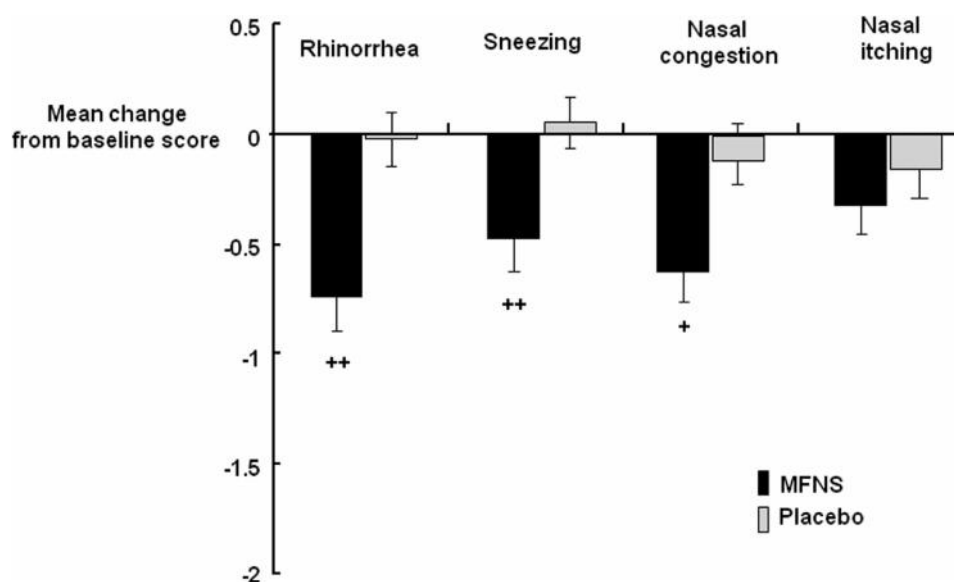


Figure 3. Comparison of the mean changes from baseline in each nasal symptom scores averaged over days 0–14. A significant decrease of each symptom score was seen in the mometasone furoate nasal spray (MFNS) group, respectively. $p < 0.05$ and $p < 0.01$ (versus placebo).

PAR patients compared with day 0 (Table 2). Among ocular symptoms, the score for watering of the eyes was significantly decreased ($p < 0.05$). The changes of each symptom score from days 0 (baseline) to 14 are compared between the MFNS and placebo groups in Fig. 3. The change from baseline was significantly larger in the MFNS group than in the placebo group with respect to rhinorrhea (mean change of 0.74 for MFNS versus 0.02 for placebo; $p < 0.01$), sneezing (0.48 versus 0.05; $p < 0.01$), and congestion (0.62 versus 0.09; $p < 0.01$). There were no significant differences between the MFNS and placebo groups on day 0.

QOL Score

Table 3 shows the score of each JRQLQ domain on days 0 and 14 in the MFNS and placebo groups. Administration of MFNS for 14 days improved the overall QOL score (Table 3; $p < 0.001$). The QOL scores for the usual daily activity domain ($p < 0.001$), social functions domain ($p < 0.01$), physical problems domain ($p < 0.001$), and

emotional functions domain ($p < 0.01$) on day 14 were superior to those on day 0 in the MFNS group.

Figure 4 displays the changes of the QOL score from days 0 (baseline) to 14. Comparison of the change from baseline between the MFNS and placebo groups showed a significant difference for the three domains of usual daily activities (mean change of 1.71 for MFNS versus 0.55 for placebo; $p < 0.01$), outdoor activities (0.24 versus 0.41; $p < 0.01$), and social function (0.53 versus 0.26; $p < 0.05$). The overall QOL score (sum of the scores of all domains) was significantly decreased in the MFNS group (0.42 versus 0.02; $p < 0.05$). There was no difference in each domain between the MFNS and placebo groups on day 0.

Sleep Disturbance

The JESS score was compared between days 0 and 14 in the MFNS and placebo groups. In the MFNS group, it showed no significant difference between days 0 (10.96 ± 0.61) and 14 (10.23 ± 0.56). In the placebo

Table 3 QOL scores

	MFNS				Placebo			
	Day 0		Day 14		Day 0		Day 14	
Usual daily activities	4.90	4.25	3.19	3.98***	4.40	0.57	4.95	0.60
Outdoor activities	0.91	1.06	0.67	1.34	0.60	0.17	1.02	0.21
Social functions	1.40	1.72	0.86	2.00**	1.02	0.22	1.28	0.25
Physical problems	2.16	1.92	1.22	1.63***	2.21	0.28	2.00	0.28
Emotional functions	2.81	3.36	1.78	2.78**	2.43	0.40	2.50	0.45
Overall QOL score	2.79	0.77	2.40	0.94***	2.91	0.11	2.91	0.11

Mean standard error.

** $p < 0.01$ compared with day 0; *** $p < 0.001$ compared with day 0.

MFNS mometasone furoate nasal spray; QOL quality of life.

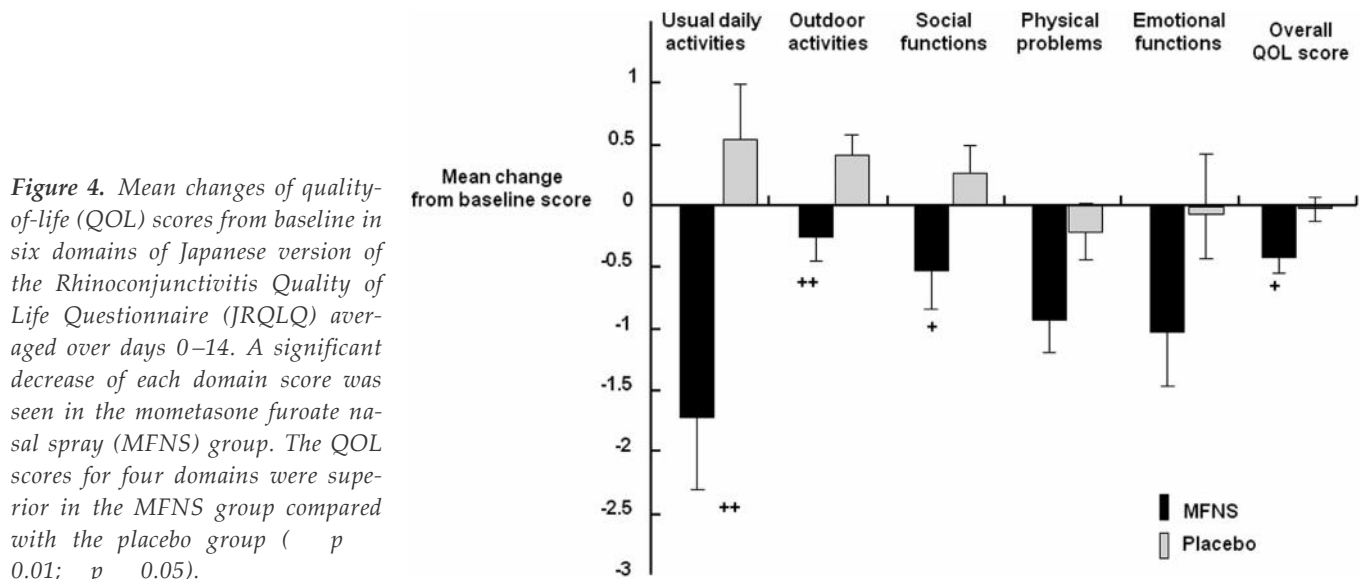


Figure 4. Mean changes of quality-of-life (QOL) scores from baseline in six domains of Japanese version of the Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ) averaged over days 0–14. A significant decrease of each domain score was seen in the mometasone furoate nasal spray (MFNS) group. The QOL scores for four domains were superior in the MFNS group compared with the placebo group ($p < 0.01$; $p < 0.05$).

group, it also showed no change between days 0 (11.11 $\pm$ 0.53) and 14 (10.79 $\pm$ 0.53).

Because it is difficult to observe changes of mild sleep disturbance, changes investigated after the subjects were classified into two subgroups based on the JESS score, *i.e.*, ≥ 12 points (indicating abnormal sleep) and < 12 points (Fig. 5).¹¹ Consequently, in subjects from the MFNS group with a score of ≥ 12 points (indicating moderate-to-severe sleep disturbance), the JESS score showed a significant decrease from days 0 to 14 (15.73 $\pm$ 0.54 versus 13.73 $\pm$ 0.67; $p < 0.01$).

Nasal NO

NO was measured on days 0 and 14 in the MFNS and placebo groups. Figure 6 displays the changes of nasal NO. There was a significant decrease from 113.9 $\pm$ 6.7 to 94.4 $\pm$ 5.7 ppb ($p < 0.01$) in the MFNS group. On the other hand, there was no significant decrease in the placebo group (112.0 $\pm$ 6.6 ppb versus 100.7 $\pm$ 6.4 ppb). In the MFNS group, both nasal FENO (176.9 $\pm$ 10.4 ppb versus 149.9 $\pm$ 8.6 ppb; $p < 0.01$) and oral FENO

(63.0 $\pm$ 5.6 ppb versus 55.4 $\pm$ 5.0 ppb; $p < 0.001$) were significantly decreased.

Comparison of nasal NO and the scores for each nasal symptom showed that nasal NO was most closely correlated with the TNSS ($r = 0.2015$; $p < 0.05$). Therefore, the change of nasal NO was investigated in more detail after the subjects were stratified into those with a TNSS of ≥ 4 points and those with a TNSS of < 4 points on day 0 (Fig. 7). Consequently, among the 30 subjects with a TNSS of ≥ 4 points, nasal NO was significantly decreased in the MFNS group (121.7 $\pm$ 10.0 ppb versus 97.4 $\pm$ 9.0 ppb; $p < 0.01$), but showed no significant change in the placebo group (119.7 $\pm$ 11.2 versus 102.1 $\pm$ 9.9). Among the 26 subjects with a TNSS of < 4 points, however, nasal NO was not significantly decreased in the MFNS group or the placebo group (data not shown).

Adverse Events

None of the 57 subjects had MFNS-related adverse events of any relevance.

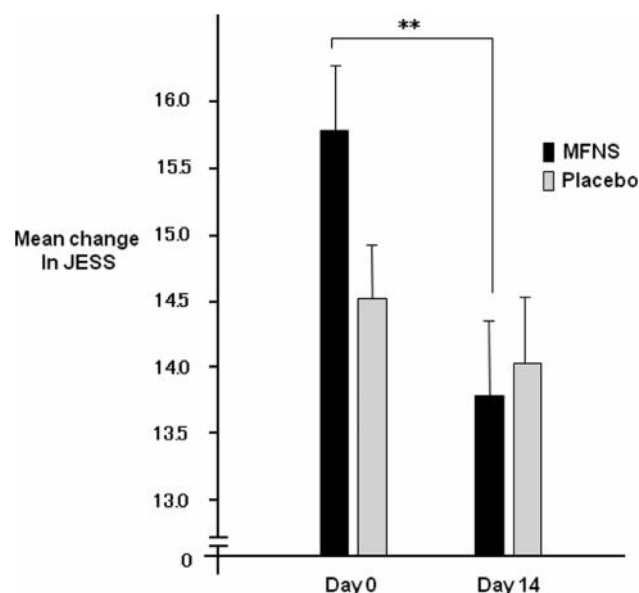


Figure 5. Effect on the sleepiness scale in the group with sleep disturbance. Sleepiness scores were calculated on days 0 and 14 using Japanese version of the Epworth Sleepiness Scale (JESS). A significant decrease of the sleepiness scale was seen in the mometasone furoate nasal spray (MFNS) group with severe sleep disturbance (** $p < 0.01$).

DISCUSSION

Subjective nasal symptoms, QOL scores, and moderate-to-severe sleep disturbance showed significant improvement with MFNS therapy in this study. MFNS also improved nasal NO, an objective indicator of AR. Consistent with previous western studies assessing nasal symptoms¹⁴, Japanese patients with PAR receiving MFNS showed significant reduction of TNSS over the 24-hour dosing interval in the present study. Among the symptoms investigated, all nasal symptoms showed significant improvement in the MFNS group. The newest information about MFNS indicates that this drug also improves ocular symptoms, although it is an INS.¹⁵ The score for watering of the eye significantly was improved by MFNS in this trial.

Evaluating QOL is a recent recommendation for patient-reported outcome assessment in clinical trials of AR.¹⁶ We found that administration of MFNS for 14 days improved the overall QOL score in this study, as reported previously.⁷

Another point about MFNS is the improvement of sleep disturbance. Nasal congestion is rated as the most bothersome symptom of PAR and is associated with excessive daytime sleepiness.¹⁷ Meltzer *et al.* performed a randomized, double-blind, placebo-controlled, clinical trial of MFNS in patients who had PAR and rhinitis-disturbed sleep.¹⁸ Significant improvement was achieved by MFNS for TNSS, nasal symptoms, objective measures of nasal flow, sleepiness,

QOL score, and work absenteeism. However, differences between the MFNS and placebo groups with regard to the apnea-hypopnea index and snoring were not significant. They concluded that improved sleep quality due to MFNS treatment does not depend on changes of airflow dynamics in the oropharyngeal region. In this trial, improvement of sleep disturbance was investigated after our subjects were stratified by severity. As a result, it was confirmed that the JESS score of the patients with moderate-to-severe sleep disturbance was significantly improved in the MFNS group compared with the placebo group.

We measured nasal NO as an objective parameter for evaluation of nasal inflammation. The American Thoracic Society recommends aspiration at a constant flow rate from one nostril with gas entrained *via* the other nostril.¹³ Such gas samples are isolated from the influence of the lower respiratory tract, because the velum is closed to prevent leakage of nasal NO *via* the posterior velopharyngeal aperture. With our method of measuring nasal NO by exhalation through both nostrils, the problem is contamination with NO from the lower respiratory tract. We found that nasal FENO levels were significantly higher compared with oral FENO levels, which is in agreement with several previous studies,^{19,20} and nasal FENO and oral FENO levels were not correlated with each other. Therefore, oral FENO was subtracted from nasal FENO to calculate nasal NO. The on-line method used in this study for oral FENO and nasal FENO measurement is highly reproducible and easy for both the subject and the researcher to perform.

It has been reported previously that nasal NO levels are significantly higher in AR patients than healthy volunteers.^{21,22} However, several researchers have found that nasal NO is not significantly correlated with the symptoms of AR.^{21,23} In this trial, nasal NO was significantly correlated with TNSS, and among the individual symptoms investigated, the nasal congestion score was also significantly correlated with nasal NO (data not shown). It is a well-known fact that expiratory airflow through the nasal cavity is negatively correlated with nasal FENO.²⁴ In our preliminary study of nasal NO during the cedar pollen season in patients with SAR-JC, nasal NO was also correlated with the TNSS and with the nasal congestion score (data not shown). It has also been reported that investigation of clinical correlations based on the measured values of nasal FENO is useful.^{19,20}

It has already been reported that nasal NO is decreased by administration of INSs.^{22,23} On the other hand, nasal NO is not decreased by administration of antihistamines²¹ or antileukotrienes.²⁵ These findings were obtained presumably because nasal NO reflects inflammation of the nasal and paranasal cavities and because the anti-inflammatory effects of INSs are

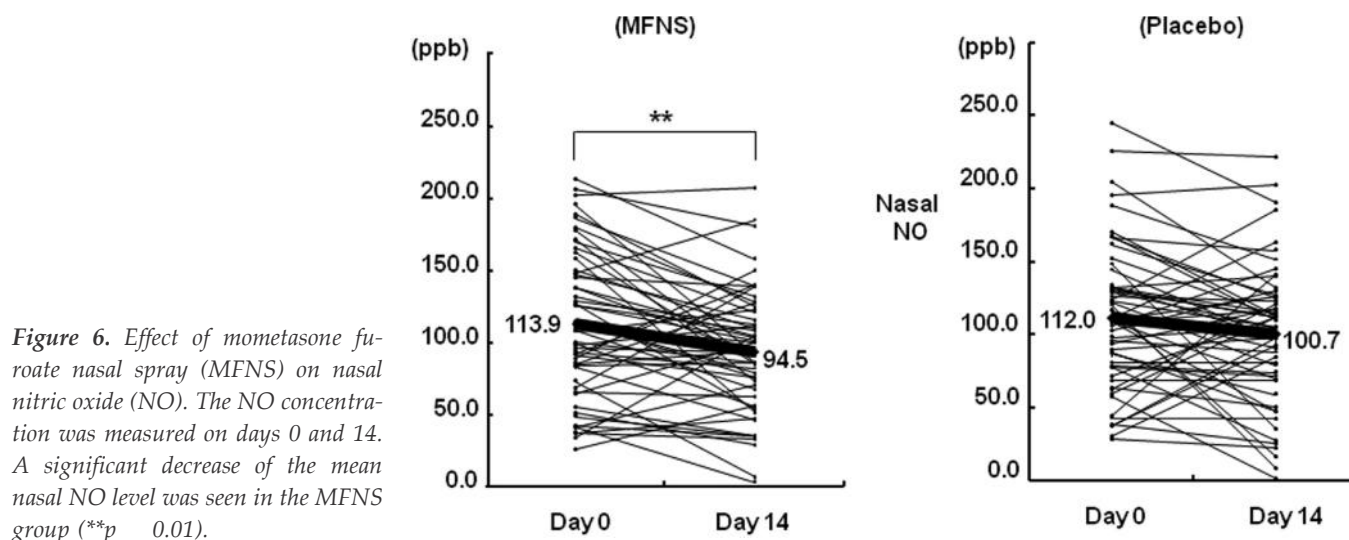


Figure 6. Effect of mometasone furoate nasal spray (MFNS) on nasal nitric oxide (NO). The NO concentration was measured on days 0 and 14. A significant decrease of the mean nasal NO level was seen in the MFNS group (** $p < 0.01$).

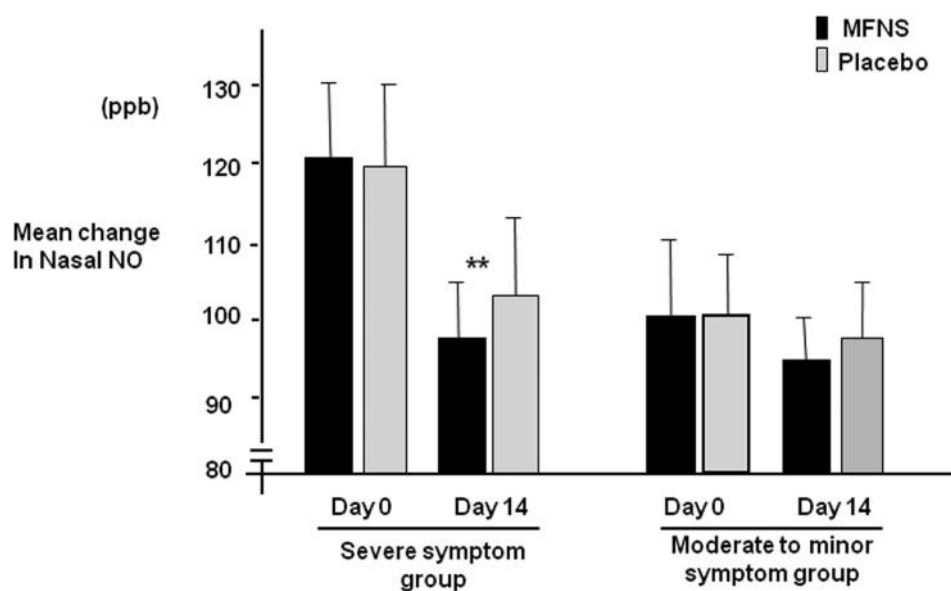


Figure 7. Effect on nasal nitric oxide (NO) in the patients with severe nasal symptoms. The NO concentration was measured on days 0 and 14. A significant decrease of the mean nasal NO level was seen in the mometasone furoate nasal spray (MFNS) group (** $p < 0.01$).

stronger than those of antihistamines and antileukotrienes. Corticosteroid nasal sprays such as MFNS exhibit an anti-inflammatory effect by inhibiting the release of inflammatory mediators, cytokine production, and inflammatory cell infiltration into the nasal mucosa, and by decreasing vascular permeability or by enhancing the apoptosis of inflammatory cells.³ MFNS inhibits eosinophil infiltration not only into the mucosa of inferior nasal concha but also into that of the olfactory cleft when administered to patients with PAR for 2 weeks.²⁶

In conclusion, the present trial shows that 2 weeks of treatment with MFNS improved nasal symptoms, QOL, and sleep disturbance, suggesting that appropriate use of MFNS is useful for Japanese PAR patients.

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