Role of antioxidants on the clinical outcome of patients with perennial allergic rhinitis

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ABSTRACT

Background: *Antioxidants have a preventive or therapeutic role in oxygen free radical–mediated cell and tissue damage. The study aimed to investigate the therapeutic effects of antioxidants and intranasal steroid fluticasone furoate (FF) on the clinical outcome of patients with perennial allergic rhinitis.*

Methods: *Subjects with perennial allergic rhinitis (n = 61) were randomly divided into two groups, group A (n = 30) received FF and group B (n = 31) received FF with antioxidants for 6 weeks. Nasal and ocular symptoms were evaluated weekly by using a four-point categoric scale. The efficacy of the study drug was assessed based on the mean change from baseline of the total daytime nasal symptom scores, total nighttime nasal symptom scores, and the composite symptom scores.*

Results: *The combined therapy (FF with antioxidants) resulted in marked improvements ($p \leq 0.05$) in the mean total daytime nasal symptom scores, total nighttime nasal symptom scores, and composite symptom scores of subjects compared with ones treated with intranasal steroid (FF) alone, which highlighted the therapeutic effect of antioxidants in allergic rhinitis.*

Conclusion: *Significant improvement in clinical outcome was observed in subjects who received antioxidants along with FF. However, because this was an open-label study, the results must be interpreted with caution, and further double-blind, placebo-controlled, dose-ranging trials supplemented with different antioxidants together with intranasal steroids are suggested.*

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Allergic rhinitis (AR) represents an enormous global health burden, which affects between 10% and 20% of the world population, with an increasing prevalence over the past decade.[1] AR is a common disorder that affects people of all ages and is associated with significant impairments in quality of life, sleep, and work performance.[2,3] AR has been classified as seasonal and perennial; the former occurs seasonally due to outdoor allergens, such as mold spores and pollens of trees, grasses, and weeds during cross-pollination through wind; and the latter is associated with indoor allergens, *viz.*, cockroaches, dust-mite fecal particles, animal dander, and occupational exposure throughout the year.[4] However, these definitions are a poor reflection of real life,[5] with some pollens occurring perennially and some symptoms of perennial allergies not being present continuously.[6]

According to the Allergic Rhinitis and Its Impact on Asthma guidelines, AR is reclassified into intermittent and persistent, which is based on the duration of the symptoms.[7] The types can be further subdivided based on the severity of patient symptoms, into mild or moderate to severe. The traditional nomenclatures of seasonal and perennial AR (PAR) are retained herein to allow a direct discussion of published data.[7]

AR involves inflammation of mucous membranes of the nose and eyes, and is characterized by a complex interaction of inflammatory mediators but ultimately is triggered by an immunoglobulin E–mediated response to an extrinsic antigen,[8] with symptoms that include rhinorrhea, sneezing, nasal congestion, itching of the nose and palate, and ocular symptoms (itching, tearing, and congestion). Clinical examinations revealed pale nasal mucosa, with swollen, edematous turbinates, and clear nasal secretions.[9]

Pharmacotherapies are composed of oral and intranasal antihistamines, mast cell stabilizers, leukotriene inhibitors, decongestants, intranasal anticholinergics, and intranasal steroids (INS).[10] INS are recommended as first-line treatment for patients with moderate-to-severe symptoms of allergic rhinitis (AR)[11] and has been proven to improve all nasal symptoms and patients' quality of life.[12] INS are more effective compared with oral or intranasal antihistamines and the antileukotrienes; however, they are comparable with or equivalent to the combination of antihistamine plus antileukotriene.[12–15]

The mode of action of steroids attributes to anti-inflammatory potential; steroids work by penetrating the plasma membrane and binding to the cytosolic

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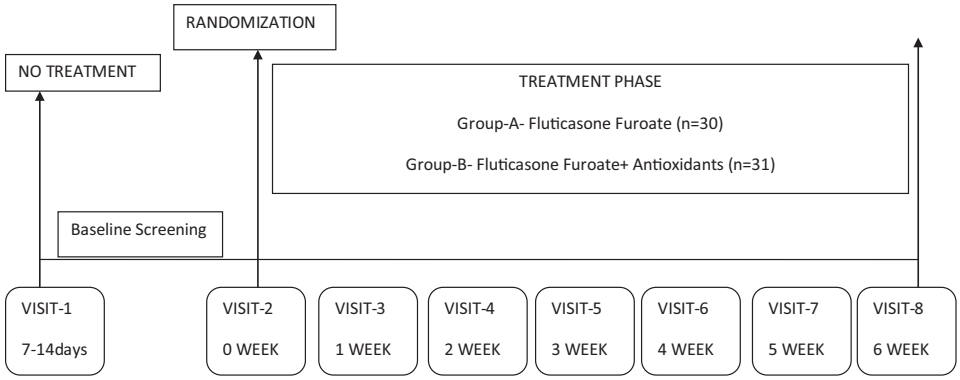

Figure 1. *Study design.*

glucocorticoid receptor (GR). After glucocorticoid receptor binding, the steroid–glucocorticoid receptor complex translocates into the nucleus and binds the DNA at the glucocorticoid response elements in the 5′-upstream region of the steroid responsive genes. The transcriptional activation of the anti-inflammatory genes or the repression of the proinflammatory transcription factors lead to the inhibition of the transcription of the inflammatory genes.[13] A study demonstrated that despite of the efficacy of INS, only 60% of the subjects showed improved symptoms and relief, thereby clearly indicating the need for improved treatment modalities. Henceforth, ancillary treatments to improve the efficacy of INS have become the main focus of research.[16]

Reactive oxygen species (ROS) play an important role in biologic function. Initially, the generation of ROS was viewed as indiscriminate and random and their targets as primary determinants of disease and aging. However, there is research that demonstrated that ROS generation is a normal physiologic phenomenon, particularly for proper immunocompetence and in coordination and activation of numerous signal transduction pathways.[17] Under controlled conditions, when produced in the correct amounts, at the right place and time, these ROS are highly beneficial for the organism and are critical for cell homeostasis.

There are studies that report that the cells that line the nasal mucosa in patients with AR produce a variety of ROS that disturb the equilibrium between oxidants and antioxidants, and thus weaken one's antioxidant defense system leading to the pathogenesis of asthma and AR[18–20] The association between chronic inflammation and oxidative stress is well documented. Elevated levels of ROS, such as hydroxyl radicals, peroxides, and superoxides, may induce a variety of pathologic changes that are highly relevant in nasal and airway mucosa. These changes include lipid peroxidation, increased airway reactivity, enhanced nasal mucosal sensitivity and secretions, production of chemoattractant molecules, and increased vascular permeability.[21,22] The role of oxidative stress in AR is not well studied but is likely to be similar to that in asthma.[23] Because several oxidants and antioxidants are likely to be involved in the pathogenesis of the inflammatory process in AR, the present study was planned to evaluate the role of antioxidants along with INS (fluticasone furoate [FF]) on the clinical outcome of patients with PAR.

METHODS

Study Design

This prospective, randomized, open, parallel group study was conducted between April 2013 and March 2015 at the outpatient department of Gian Sagar Medical College and Hospital, Patiala, Punjab, India. The protocol was approved by the institutional ethics committee of Gian Sagar Medical College and Hospital. The study was conducted in accordance with the International Conference on Harmonization-Good Clinical Practice guidelines, with written informed consent from each subject before enrollment in the study. The study consisted of a 2-week screening period followed by a 6-week treatment period (Fig. 1). The visits were scheduled periodically after 1 week for 6 weeks. The subjects were randomly allocated by using random number tables to receive FF in group A, which served as the control group, and FF and antioxidants in group B, which served as the treatment group.

Patients Selection

Subjects between 18 and 55 years of age with a clinical history of PAR and at least two nasal symptoms (sneezing, rhinorrhea, nasal obstruction, itching) with eosinophilia on blood smear and/or nasal smear for at least 6 months in the previous 2 years participated in the screening period for a minimum of 7 days and a maximum of 14 days. Subjects were excluded from participation in the study if a significant concomitant medical condition (renal, hepatic, or cardiovascular disease) was evident, including uncontrolled disease of any body system; severe physical nasal obstruction (polyps, displaced septum) or injury; asthma, rhinitis medicamentosa or bacterial or viral infection within 2 weeks of the study; acute or

significant chronic sinusitis; infection of the nose; any psychiatric disorder; or pregnancy and lactation. Patients were also excluded if they had received a systemic or inhaled corticosteroid in the past 8 weeks, INS in the last 4 weeks before the first visit, other allergy medications (oral, topical antihistamines, decongestants) within specified time frames chosen to ensure no continued effect on symptoms or any other medications that could affect allergic rhinitis (AR) or the effectiveness of the study drug.

Therapeutic Protocol

The subjects who fulfilled the inclusion and exclusion criteria and the minimum symptoms criteria were randomized into two groups: group A received 110 μg of FF once daily with the first dose administered at the clinic after device demonstration; and group B received 110 μg FF along with oral administration of an antioxidant preparation that contained β- carotene (provitamin A) 20 mg (26,000 IU), vitamin C (ascorbic acid) 200 mg, vitamin E 200 mg (200 IU), and selenium 50 μg. A physical examination for nasal secretions and turbinate swelling was done when the patients returned to the clinic weekly for 6 weeks (visits 2 to 8). The patients were told to record on diary cards any medical conditions that they experienced.

Outcome Measurements

The primary outcome measurement was the mean change of the total daytime nasal symptom score (PDTS), which was defined as the average score of four daytime nasal and three ocular symptoms. The secondary outcome measurements were the mean changes of the total nighttime nasal symptom scores (PNTS) and the composite symptom scores (PCS) (average score of day- and nighttime nasal symptom score). The patients were clinically examined at each visit by the same clinician (B.C.) to eliminate interobserver variations and to enhance the credibility of the nasal examinations of the subjects.

Daily Rhinitis Diary Card

The diary contained four daytime nasal symptoms (rhinorrhea, sneezing, itching, and congestion) and three ocular symptoms (itching, watering, and congestion) and three nighttime nasal symptoms (nasal congestion on awakening, difficulty in going to sleep, and nighttime awakening). The severity of PAR symptoms was rated on a scale that ranged from 0 (none) to 3 (severe) for both the daytime (the diary card was completed in the evening) and the nighttime (the diary card was completed on awakening). The ratings of the symptoms were as follows: 0, not noticeable; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms. The rating was done by the patients themselves to increase the credibility.

Statistical Analysis

The results were expressed as mean (standard deviation [SD]) of 61 subjects. Statistical analysis of the results involved nonparametric tests (χ^2 test and the Mann Whitney U test) and parametric tests (two-tailed unpaired Student's t-test). The nominal variables were compared by using χ^2 analysis. The Student's t-test was used for the comparison of the group means for the normally distributed data, and the Mann-Whitney U test and rank test were used for the nonnormally distributed data. The values with $p \leq 0.05$ were considered statistically significant.

RESULTS

Study Population

A total of 75 subjects with PAR were screened for the study. Of the total, 66 subjects confirmed to the inclusion/ exclusion criteria and were eligible for the study. Ninety-two percent of the subjects completed the study. Five patients (two in group A and three in group B) did not report for the follow-up. Group A (FF) was composed of 30 subjects (17 men, 13 women), with a mean (SD) age of 47.2 $\pm$ 14.24 years (range, 18–55 years); group B (FF and antioxidants) was composed of 31 subjects (18 men, 13 women), with a mean (SD) age of 44.7 $\pm$ 11.45 years (range, 18–55 years) (Table 1). There was no statistically significant ($p \geq 0.05$) difference between the two groups regarding age and sex, and they had comparable clinical profiles.

Efficacy

Primary Efficacy. The primary efficacy measurement was the mean PDTS change from the basal values (0 week) over the entire treatment regime (6 weeks). At baseline, the mean (SD) scores of PDTS were similar in groups A and B (2.50 $\pm$ 0.20 and 2.50 $\pm$ 0.21, respectively), which highlighted that both the groups were comparable. The symptoms showed a gradual improvement up to 2 weeks ($p \geq 0.05$) and markedly improved from the second week to the end of the 6 weeks ($p \leq 0.05$) in both treatment groups. A marked improvement ($p \leq 0.05$) in overall mean scores of clinical outcome of patients (0–6 weeks) in group B (1.73 $\pm$ 0.51) was observed in contrast to group A (1.94 $\pm$ 0.44) (Table 1). However, group B (1.26 $\pm$ 0.25) showed a greater improvement ($p \leq 0.05$) in the mean scores at end of the last week (6 week) of treatment period in comparison to group A (1.52 $\pm$ 0.32) (Fig.2).

Secondary Efficacy. Secondary efficacy measurement was the mean PNTS change from the baseline (0 week) over the entire treatment period of 6 weeks. Significant improvement ($p \leq 0.05$) in mean (SD) PNTS in patients in group B (1.63 $\pm$ 0.49) who were

Table 1. **Efficacy of antioxidants and intranasal steroids on clinical outcome of group A (n = 30) and group B (n = 31)**

Characteristics		Test Value	p Value
Age, mean (SD), y*			
Group A	47.2 ± 14.24	0.75#	0.96#
Group B	44.7 ± 11.45		
No. men:women§			
Group A	17:13	0.012#	0.91#
Group B	18:13		
PDTS, mean (SD)*¶			
Group A	1.94 ± 0.44	4.46*‖	0.004*‖
Group B	1.73 ± 0.51	1.66¶‖	0.048¶‖
PNTS, mean (SD)*¶			
Group A	1.83 ± 0.41	4.12*‖	0.006*‖
Group B	1.63 ± 0.49	0.042¶‖	0.042¶‖
PCS mean (SD)*¶			
Group A	1.89 ± 0.42	4.37*‖	0.004*‖
Group B	1.68 ± 0.51	0.06¶‖	0.017¶‖

SD = Standard deviation; PDTS = total daytime nasal symptom score; PNTS = total nighttime nasal symptom score); PCS = total composite symptom score.
**Unpaired Student's t-test.*
#Nonsignificant.
§The χ^2 test.
¶Mann-Whitney U test.
‖Significant at $p \leq 0.05$.

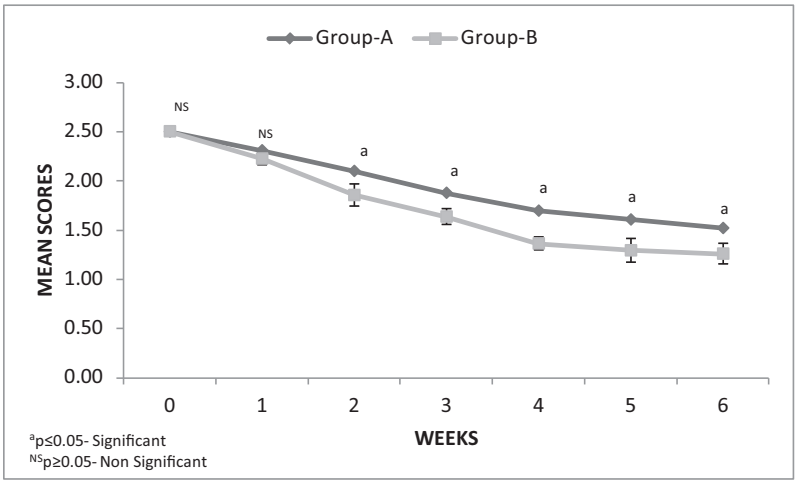

Figure 2. *Weekly mean scores of daytime nasal symptom scores.*

treated with FF and antioxidants in contrast to group A (1.83 ± 0.41) who were treated with FF only occurred (Table 1). The positive trend in improvement of symptoms in both treatment groups is shown in Fig. 3. The maximal decrease in the mean (SD) scores in PNTS was observed at the end of 6 weeks, with mean (SD) values of 1.20 ± 0.27 and 1.42 ± 0.19 in group B and group A, respectively.

Composite Efficacy

The composite symptom score (average [SD] score of day- and nighttime nasal symptom scores) of both treatment groups (group B, 1.68 ± 0.51; group A, 1.89 ± 0.42) significantly ($p \leq 0.05$) improved by the end of the study (Table 1). Marked improvement in symptoms was observed in both the groups; however, the outcomes were more pronounced in group B (1.23 ± 0.26) treated with blends of INS and antioxidants contrary to group A (1.47 ± 0.27) treated singly with FF at the end of 6 weeks (Fig. 4). The p values for the primary, secondary, and composite symptom scores on a weekly basis for the entire treatment regime clearly indicated that the symptoms markedly improved ($p \leq 0.05$) in group B

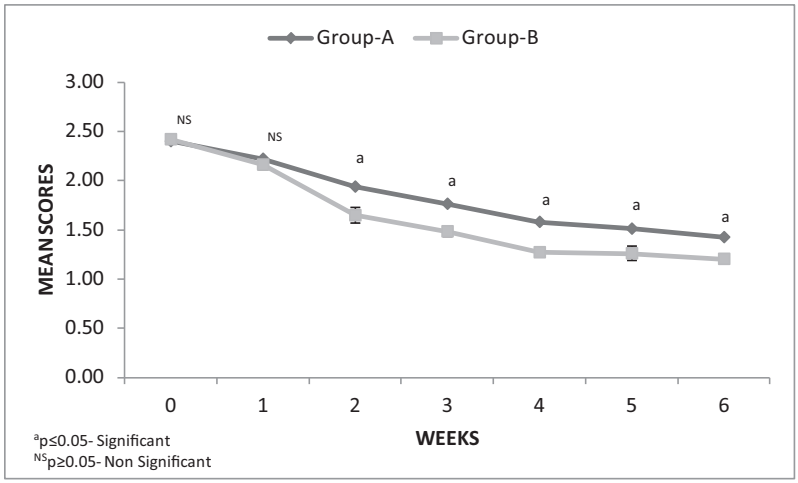

Figure 3. *Weekly mean scores of nighttime nasal symptom scores.*

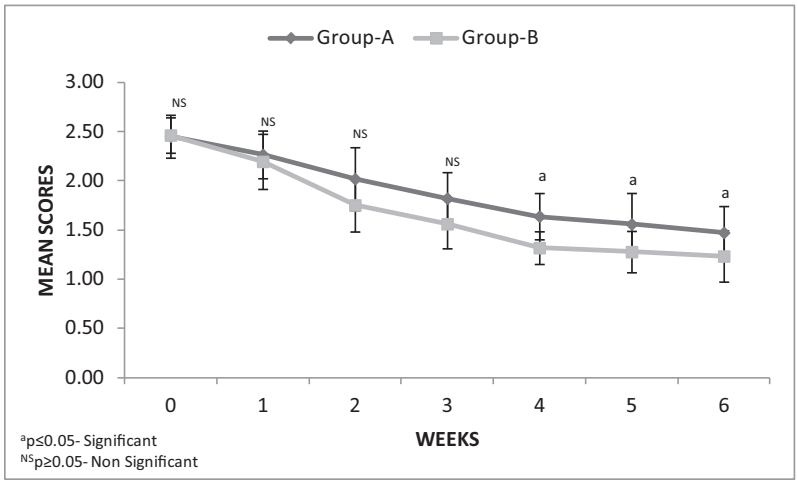

Figure 4. *Weekly mean composite scores of day- and nighttime nasal symptom scores.*

Table 2 **The *p* values (by using the unpaired Student's *t*-test) for primary, secondary, and composite symptom scores on a weekly basis**

	0	1	2	3	4	5	6
PDTS	0.91*	0.26*	0.005#	0.002#	5.65×10^{-7}	0.0001#	0.001#
PNTS	0.64*	0.43*	0.0001#	1.99×10^{-5}	1.24×10^{-8}	0.00002	0.0005#
PCS	0.87*	0.32*	0.18*	0.11*	0.05#	0.03#	0.04#

PDTS = total daytime nasal symptom score; PNTS = total nighttime nasal symptom score; PCS = composite symptom score.
**Nonsignificant at $p \geq 0.05$.*
#Significant at $p \leq 0.05$.

in contrast to group A toward the end of 6 weeks (Table 2).

Safety and Tolerability

Twenty-seven subjects (90%) in group A and 29 subjects (93%) in group B did not report any adverse effects of the study drugs. Five subjects (three in group A and two in group B) reported mild symptoms, *e.g.*, sneezing, stinging, burning sensation. None of the symptoms were severe enough to warrant the termination of the treatment, reduction in the dose, or other additional therapies or medications.

DISCUSSION

Oxygen is vital for life processes, yet aerobic metabolism is toxic. This is one of the major paradoxes of aerobic life. The detrimental effect of oxygen is not due to its own reactivity, which is rather feeble, but due to its reduction to form water that proceeds by a series of

a single electron transfer down the mitochondrial respiratory chain and generate reactive species. Therefore, the cells under an aerobic environment are always threatened with the insult of ROS. These species are produced at low concentrations under normal physiologic conditions, and the damage that they cause to cells is constantly repaired. However, under pathologic conditions, there may be increased production of free radicals coupled with increased consumption or decreased production of the endogenous antioxidant defense system, which results in an imbalance between prooxidant and antioxidant factors, and results in "oxidative stress."[24] The body adapts to the slight imbalance and induces the production of extra endogenous antioxidant defense enzymes. However, a severe imbalance results in excess production of ROS and free radicals, which thus weakens the system further.

AR is an inflammatory disorder of the upper airways. ROS contribute to the pathogenesis of allergic disorders.[25,26] The presence of chronic inflammation in the epithelium of the upper airways in AR could contribute to the development of the considerable persistent oxidative stress. Airway inflammatory cells are the source of increased ROS production.[26,27] Antioxidants generally found in the epithelial lining cells and fluids of the airways include superoxide dismutase, glutathione peroxidase, catalase, thioredoxin, the iron-binding proteins lactoferrin and transferrin, the copper-binding protein ceruloplasmin, and the low-molecular-weight antioxidants (*e.g.,* glutathione, urate, vitamin E, and vitamin C).[26–28]

Ascorbic acid is physiologically available in the respiratory tract and may cause a reduction of negative effects caused by oxidative attack on tissues during inflammation. It prevents the secretion of histamine by white blood cells and increases its detoxification.[29] A study reported an exponential increase in histamine levels with a concomitant decrease in plasma ascorbic acid levels,[30] which thus confirmed an inverse relationship with histamine levels, henceforth, decreasing the symptoms of AR. Furthermore, vitamin C stimulates the immune system by enhancing T-cell proliferation in response to infections. These cells are capable of lysing infected targets by producing large quantities of cytokines and by helping B cells to synthesize immunoglobulins to control the inflammation reaction. Moreover, vitamin C plays an important role in lipid peroxidation. Studies have reported that plasma devoid of vitamin C has an increased rate of lipid peroxidation, which indicated therapeutic potential against free radical–mediated diseases.[31,32]

Vitamin E is a major lipid soluble antioxidant present in all cellular membranes and can act directly against a variety of oxygen free radicals, including peroxy radicals, superoxide radicals, and singlet oxygen, and which thereby protects against lipid peroxidation. Selenium, an essential component of glutathione peroxidase, is a part of the body's antioxidant defense system and plays an important role in the decomposition of hydrogen peroxide and lipid peroxides.[33] Selenium acts synergistically with vitamin E to protect cell membranes from damage caused by dangerous naturally occurring substances known as free radicals. Vitamin A designates a group of retinoid compounds with the biologic activity of all *trans*-retinol. Retinoids usually consist of four isoprenoid units with five conjugated carbon-carbon double bonds. One study reported that vitamin A consumption increases the repair of mucosal epithelium that is damaged by inflammation and prevents the oxidative damage in AR.[34]

There are a number of pharmacotherapies available for AR that are composed of oral and intranasal H_1 antihistamines, decongestants, intranasal corticosteroids, anticholinergics, cromolyn, and leukotriene receptor antagonists.[9,35,36] The INS have been the focus of research for a long time and have been effective against moderate-to-severe disease because all the major symptoms of AR are relieved with their usage[12] However, a study has indicated that ~60% of subjects achieve relief from INS, which indicates the need for additional treatment to improve its efficacy.[16]

A diet rich in antioxidants has been associated with a low prevalence of allergic diseases.[37,38]A strategy for designing well-balanced antioxidant therapies based on both reducing endogenous ROS production and increasing the total antioxidant capacity of human cells may prove useful in the prevention of AR. Thus, a comprehensive study was planned to find the efficacy of antioxidants along with FF on the clinical outcome of patients with PAR.

The study demonstrated that treatment with FF, along with antioxidants, is effective in alleviating the nasal symptoms and providing relief from ocular symptoms in the subjects with PAR. The response to treatment was comparatively gradual initially but continued at a consistent rate over the course of the study. The observed effects of FF on nasal symptoms result from topical action through its absorption into the nasal mucosa. Kaiser *et al.,*[39] reported that fluticasone furoate therapy for 2 weeks results in clinical improvement in overall quality of life by reducing symptom severity. The antioxidants, however, strengthen the defense system and prevent oxidative stress, the prime etiologic factor for PAR. A study concluded that high plasma carotenoid concentration, which reflects a diet rich in fruits and vegetables, has a protective effect on AR.[40] Similar results demonstrated in another study, which revealed elevated plasma total antioxidant status (TAS) and total oxidative status (TOS) in children with AR.[41] Similarly Nagel *et al.,*[42] reported a decreased risk of adult-onset hay fever with increasing

intake of vitamin E. Sequeria *et al.*,[43] demonstrated a significant decrease in vitamin C and total antioxidant levels in patients with AR.

In the present study, a combination of antioxidants and FF was effective in improving the PDTS, PNTS, and PCS mean scores in patients with PAR. The combined therapy with antioxidants and FF significantly improved the PAR symptoms compared with FF administered alone. Similar results were obtained in a previous study that demonstrated the efficacy of addition of antioxidants to INS (FF) in the treatment of AR.[44] Overall, no safety and tolerability issues of clinical importance were identified. A few adverse symptoms (sneezing, burning, stinging sensation) associated with treatment were mild and were similar to those reported in earlier studies.[45,46]

In sum, we showed that the combination of FF and antioxidants has beneficial effects beyond those of FF alone. We speculated that antioxidants may have a therapeutic role in limiting the damage caused by excess free radical generation and, consequently, oxidative stress built up within the nasal mucosa in AR. The study had limitations, due to subjective evaluation of outcome, but the results are noteworthy. Furthermore, this was an open label study owing to a paucity of funds. To evaluate the efficacy, a double-blind study with placebo control and a larger group would have been ideal. Further studies could use different antioxidants in different doses. The development of such a combination should be pursued at a larger level with increased numbers of responders and an increased duration of study.

CONCLUSION

This study was conducted to investigate the therapeutic effect of adding antioxidants to standard steroid therapy for AR. Analysis of the results indicated that antioxidants resulted in a improved clinical outcome; thus, antioxidants may play a major role in the prevention and treatment of AR. However, more comprehensive clinical studies are needed.

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