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Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, **2014**, *13*, 75-82

Evaluation of Topical Black Seed Oil in the Treatment of Allergic Rhinitis

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Abstract: *Background*: Allergic rhinitis (AR) is the most common manifestation of atopic reaction to inhaled allergens. It is a chronic inflammatory disease which may first appear at any age, but the onset is usually during childhood or adolescence. Up to date there is no curative treatment for this disorder and most of the drugs that were used for treatment only can induce symptomatic relief and some of them have side effect and can cause withdrawal symptoms. *Objective*: To evaluate the therapeutic efficacy of the *Nigella sativa* (NS) extract as treatment approach for allergic rhinitis. *Patients & Methods*: A total of 68 patients with AR were included in the study, of them 19 patients were with mild symptoms, 28 patients were with moderate symptoms and 21 patients were with severe symptoms. Each group was subdivided into active and control subgroups. To prove that the patient's symptoms were allergic in nature, skin test was performed for all patients. Any individual with negative skin test was excluded. The individuals in the active group received *N. sativa* oil and the control group individuals received ordinary food oil in the form of nasal drops for 6 weeks. *Results*: After the 6 weeks treatment course, 100% of the patients in the mild active group became symptoms free; while in moderate active group 68.7% became symptoms free and 25% were improved; while in severe active group 58.3% became symptoms free and 25% were improved. In addition, 92.1% of total patients in the active group demonstrated improvement in their symptoms or were symptoms free, while the corresponding value was 30.1% in the control group (P=0.000). At the end of 6 weeks of treatment with topical use, the improvement in tolerability of allergen exposure in active group became 55.2% which was significant (P=0.006) as compared with control group which was accounted for 20% at the same time. *Conclusion*: Topical application of black seed oil was effective in the treatment of allergic rhinitis, with minimal side effects.

Keywords: Allergic rhinitis, black cumin, IgE, iraq, medicinal plant, *Nigella Sativa*, seeds, tikrit.

INTRODUCTION

Allergic rhinitis, is an inflammation of the nasal mucosal in response to natural allergen exposure, and is a common health problem worldwide affecting 10-25% of the population [1]. Extensive research done recently has established this fact that there is a epidemiologic and therapeutic linkage present between AR and asthma [2]. This fact is further proven by number of epidemiologic studies done worldwide. In a review of five large studies which were performed on children and adults, [3] the prevalence of asthma ranged from 3.6% to 5% in subject without Allergic Rhinitis whereas those with history of Asthma showed frequency of 10.8% to 32%. Similarly in a 23 year follow-up study conducted among university students, [4] asthma frequency was found to be 10.5% among those with AR, and 3.6% in those without with out AR. In addition, the reported lifetime prevalence of AR among adults with asthma demonstrated varied range from 50% to 100%, depending upon the type of study design used and geographical area where study was conducted [5].

Asthma and AR are both inflammatory diseases of the airways. Due to similarity in epidemiologic and pathophysiological features both allergic rhinitis and asthma are part of same syndrome, the chronic allergic respiratory syndrome [6]. A report of the American Academy of Allergy, Asthma, and Immunology [7] estimated that up to 78% of patients with asthma have nasal symptoms and 38% of patients with AR have asthma. A large number of surveys have been conducted worldwide assessing the association between AR and asthma in different geographical areas, however none of them were large scale studies. A recent study in Iraq provided evidence that AR and asthma are strongly associated with each other therefore treatment approach should consider the entire airway rather than only considering nasal passage [8].

The management of allergic rhinitis comprises of 3 major categories including environmental control measures and allergen avoidance, pharmacological management, and immunotherapy. Environmental control measures and allergen avoidance involves both the avoidance of known allergens and avoidance of nonspecific, or irritant, triggers. It is also advisable to consider environmental control measures, when practical, in all cases of allergic rhinitis [9]. However, global environmental control without identification of specific triggers is inappropriate.

Although allergic rhinitis is not a life-threatening condition, various complications can occur and result in significant impairment in quality of life, [10, 11] eventually leading to increase medical cost. Fifty-four randomized, placebo-controlled studies involving more than 14,000 adults and

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1875-614X/14 $58.00+.00

1,580 children with AR met the criteria for review: 38 studies of seasonal allergic rhinitis (SAR; n = 11,980 adults and 946 children) and 12 studies of perennial allergic rhinitis (PAR; n = 3,800 adults and 366 children). The median percentage changes from baseline for total nasal symptom score for SAR were as follows: nasal antihistamines, -22.2%; oral antihistamines, -23.5%; intranasal steroids (INSs), -40.7%; and placebo, -15.0%. For PAR, the changes were as follows: oral antihistamines, -51.4%; INSs, -37.3%; and placebo, -24.8%. Data for mediator antagonists were limited [12]. The data, although limited, confirm that intranasal steroids (INSs) produce the greatest improvements in nasal symptoms in patients with seasonal AR (SAR). In addition, INSs were effective for perineal AR (PAR), but the data were of variable quality, and oral antihistamines may be equally effective for some patients. The reporting of published data should be standardized to permit better comparisons in future studies.

AR treatment should be based on the patient's age and severity of symptoms. Patients should be advised to avoid known allergens and be educated about their condition. Intranasal corticosteroids were the most effective treatment and should be first-line therapy for mild to moderate disease [13]. However, INSs were associated with some side effects such as mucus membrane atrophy and secondary bacterial infections. Moderate to severe disease unresponsive to intranasal corticosteroids needs to be treated with second-line therapies, including oral antihistamines, decongestants, cromolyn, leukotriene receptor antagonists, and non-pharmacologic therapies such as nasal irrigation. With the exception of cetirizine, second-generation antihistamines were less likely to cause sedation and impair performance [13].

Immunotherapy another option of treatment is reserved for patients with a less than adequate response to usual treatments. More recent studies in children and adults show additional positive outcomes of specific immunotherapy (SIT) with decreased tendency for additional environmental sensitization [14], and decreased incidence of asthma in treated allergic rhinitis patients [15]. Although the effectiveness of SIT in the treatment of allergic rhinitis and allergic asthma has been proven, however its delayed time of action [20] and adverse local and systemic side effects have limited its use as a treatment modality by majority of the patients [16-20].

Although there is much and convincing evidence for SIT effectiveness and efficacy from reported international studies, however only single study had prospectively investigated the real-life efficacy in Iraqi patients showing that systemic use of black seed oil was effective treatment for AR [21]. Prevention therapy including house dust mite (HDM) immunotherapy for 3 years significantly reduced symptom and medication use in AR, Asthma and patients with both conditions, and prevents the subsequent development of asthma in patients with AR. This was associated with a greater subjective improvement in asthma control [22] On the other literature does not support the use of mite-proof impermeable covers, air filtration systems, or delayed exposure to solid foods in infancy [13].

Anti allergic effects of *Nigella Sativa* a herb in nature were reported [23]. It is assumed that thymoquinone with carbonyl polymer is an active ingredient of *N. Sativa* is responsible for its antiallergic activity [24]. Recently reported study reported that the *N. sativa* usage can reduce the presence of the nasal mucosal congestion, nasal itching, runny nose, sneezing attacks, turbinate hypertrophy, and mucosal pallor during the first 2 weeks [25]. Furthermore, *N. sativa* supplementation during specific immunotherapy of AR may be considered as a potential adjuvant therapy [26] and was found to have equal therapeutic activity in relieving the symptoms of seasonal AR in comparison to cetirizine, without causing any adverse effects [27]. Similarly a recent study concluded that systemic use of *N. Sativa* extract is effective in mild and moderate allergic rhinitis symptoms reduction. Various factors may influence the response of systemic N.S treatment in allergic rhinitis and includes; multiple allergic diseases with high serum IgE level and atopic family diathesis, gender, perennial type, and old age. Side effects of *N. Sativa* extract use were trivial and easily controlled. *Nigella sativa* extract has proved to have a strong therapeutic effect in allergic rhinitis [28].

This prospective study of patients was performed to see efficacy of *Nigella Sativa* oil topical application as a treatment remedy among patients presenting with allergic rhinitis in an outpatients setting.

Objective

To evaluate the therapeutic effect of black seed extract in allergic rhinitis by nasal route.

MATERIALS AND METHODS

Black Seed Oil Extraction

The oil was extracted using Soxhlet method as described by Association of Analytical Chemistry (AOAC) method No. 963.15 [29] using petroleum ether (40-60^{o}C) for 8 hours. The constituents of the extracted oil were not performed since there were no significant variations in the chemical composition of the fixed oil of seeds grown in different areas [30].

Study Population

A total of 188 patients presenting with allergic rhinitis symptoms of different severities (mild, moderate and severe) with age ranging from 6-45 years, were included in this study (Table **1**). This was a double blinded clinical trial performed during the period between January 2009 to June 2010 in the out- patient clinic of centre of allergy in Tikrit Teaching Hospital (TTH) in Salahuldean governorate, Iraq. Patients were either referred from medical or ENT departments, or from the out patients clinics in the same hospital and also those who attended the allergy centre to have immunotherapy. A total of 68 patients were included in the study of topical black seed application for treatment of AR. After 2 weeks of withdrawal interval, topical route treatment started in 68 patients. Among these 19 patients belonged to mild group, 28 patients to moderate group and 21 patients were from severe group. Each group was further subdivided into active and control subgroups. The study protocol was approved by the ethical committee of Tikrit University College of Medi-

Table 1. Frequency distribution of patients with allergic rhinitis according to their symptoms score group.

Group	Patients Number	Sub Groups	Patients Number
Total patients	68	Active	38
		Control	30
Mild	19	Active	10
		Control	9
Moderate	28	Active	16
		Control	12
Severe	21	Active	12
		Control	9

cine, and informed verbal consent was taken from each patient included in the study.

Diagnosis of Asthma and Allergic Rhinitis

The diagnosis of allergic rhinitis was performed according to previously reported guidelines [31].

Lung Function Test

Computerized Spirometer (Autosphiror, Discom-14, Chest Corporation, and Japan) was used for measurement of FEV1 predicted percent of the patients at their enrollment in the study and when indicated according to study design.

Skin Prick Test

The skin prick test was performed in all patients and controls and was evaluated in accordance with European Academy of Allergy and Clinical Immunology subcommittee on allergy standardization and skin tests using standards allergen panel (Stallergen, France). The panel for skin test include: dust mite (*Dermatophagoides farina*, *Dermatophagoides peteronyssinus*), *Aleternaria*, *Cladosprium*, *Penicillum mixture*, *Aspergillus* mixture, Grasses mixture, Feather mixture, Dog hair, Horse hair, Cat fur, Fagacae, Oleaceae, Betulaceae, Plantain, Bermuda grass, Chenopodium and Mugworth. All tests were performed in the outpatient Asthma and Allergy Centre, Tikrit by a physician using a commercial allergen extracts (Stallergen, France) and a lancet skin prick test device. A wheal diameter of 3 mm or more in excess of the negative control was considered as positive test result.

Allergen Extracts for Skin Prick Test

Therapeutic vaccines containing allergen extracts were purchased from Stallergen, France. Both aqueous and glycenerated extracts were used to achieve a concentrate of 1:100 w/v of the mixed extract. In standardized extracts the stock formulation was prepared by tenfold dilution. Separate vial was used for allergen extract to reduce proteolysis degradation. All extracts were stored at 8 ^{0}C.

Clinical Assessment (Symptom Score)

During each visit, the patient was examined clinically for vital signs and questioned about the improvement in his day and night symptoms (Rhinorrhoea, nasal obstruction, paroxysm of sneezing, night snoring, daily physical activities, school attendance and affection of life quality). Symptom score was of 4 points scale (0-3) according to the classification of rhinitis by guidelines [31-33], thus symptoms were specified by:

- 0-No symptoms.
- Mild symptoms: Symptoms not interfere with sleep, normal daily activities, (sports, leisure), no trouble of some symptoms, sneezing (not more than 3 in each attack or paroxysm), with mild runny nose (of no more than 1hour) [32, 33].
- Moderate symptoms: Are of one or more items of the following: abnormal sleep, impairment of daily activities, (sports, and leisure), problems caused at work, at school with troublesome symptoms: longer attack > 1h. -<8 with uncomfortable stuffy, runny nose, sneering 4-10 sneeze each attack [32, 33].
- Severe symptoms: The same as moderate but more severe, more nasal blockage and sleep interference with severe distressing stuffy, runny nose for more than 8h, attack with sneeze more than 10 times each paroxysm [32,33].

Tolerability to the Exacerbating Factors

Many precipitating factors such as aeroallergen exposure, cold exposure, infection (sinusitis), drugs….etc. may precipitate the condition, so the response to the exacerbating factors were assessed in each visit.

Topical Use

Sixty eight patients were selected randomly to be treated by nasal drops of the black seed oil (Table **2**). Again, full history and physical examination were performed for each patient. Then either N.S oil or ordinary food oil (Protein 0, saturated fatty acid 12%, unsaturated fatty acid 88%, vitamin

Table 2. Tolerability of exacerbating factors in patients with allergic rhinitis receiving topical *N. Sativa* oil.

Variable	Active Group Number [%]	Control Group Number [%]	P value
Baseline frequency			
Allergen exposure	31 [81.5]	23 [76.6]	NS
URT	18 [47.3]	16 [53.3]	NS
Temperature change	15 [39.4]	11 [36.6]	NS
Smoke & irritant	12 [31.5]	6 [20.0]	NS
Percent reduction following treatment			
Allergen exposure[#]			
3 week	44.7	10.0	0.002
6 week	55.2	20.0	0.003
P value	NS	NS	
Temperature change			
3 week	18.4	6.6	NS
6 week	23.6	10.0	NS
P value	NS	NS	
Irritant			
3 week	10.5	3.3	NS
6 week	18.4	6.6	NS
P value	NS	NS	

3 week X2=9.74; 6 week X2 = 8.71.

E 35 mg) (N.S oil or ordinary food oil) was given to the patient in the form of drops (each drop container was with of about 15 ml and the patient applied 2 drops nasally (one in each nostril) 3 times a day for 6 weeks.

Clinical Assessment

During each visit, clinical assessment was done for the patients in the same way as were done for systemic use with 4 points score (0-3) according to the severity of symptoms. The score recorded for each sign and symptom.

Tolerability to the Exacerbating Factors

Any changes in tolerability to the exacerbating factors were recorded in each visit.

Side Effects

Side effects that were shown by the patients were recorded for both systemic and nasal uses.

Statistical Analysis

Chi square analytic system (X^2) with Yates correction was used to compare between active and placebo groups. However, Chi Square was calculated only if the expected cell frequencies were equal to or greater than 5. While Fisher Exact Probability Test is used if some cells were less than five. Student t test was used to determine the significance of IgE differences between the groups.

RESULTS

Sixty eight patients were randomly selected from the previously treated patients after 2 weeks of withdrawal of systemic use of the herb oil. The recruited subjects were divided into 3 groups. (Mild, moderate and severe) and then subdivided into active and control groups (Table **1**). The active group was consisted of 38 patients: of them 10 patients of mild active group, 16 patients of moderate active group and severe active group included 12 patients. While the control group consisted of 30 patients: of them, 9 patients were from mild control group, 12 patients from moderate control group and severe control group included 9 patients.

Exacerbating Factors

Frequency distribution of the exacerbating factors at the base line evaluation for nasal route treatment is shown in (Table **2**). The most common exacerbating factor was reported to be allergen exposure which accounted for 81.5%, followed by upper respiratory tract infection which was reported as 47.3%. Temperature change, cold exposure and exposure to smoke and irritants were among the least reported factors and accounted for 39.4% and 31.5% respectively. In the control group, at the base line, allergen expo-

sure was the highest exacerbating factor (76.6%) followed by URT infection and temperature which accounted for 53.3% and 36.6% respectively. Similarly smoke and irritant was reported as exacerbating factors by only 20% of control groups patients. There were no significant differences in the exacerbating factors between the active and control group. (Table **2**).

EFFECT OF NASAL TREATMENT

Symptomatic Response

The symptomatic response after 6 weeks of nasal topical treatment is shown in Table. 3. Mild active group showed significant improvement at 3 weeks as 80% (P=0.01) of the patients got benefit of treatment which was increased to 100% at 6 weeks (P=0.01) of treatment course. While in the mild control group symptomatic response was found to be 22.2% at 3rd week of treatment and increased to 44.4% at the end of the 6 week of treatment, but the overall difference was not significant.

Moderate active group showed significant improvement at the 3rdweek (P=0.008) of treatment which was accounted for 68.7%, and this increased to 93.7% at 6 weeks (P=0.002) of treatment period. In moderate control group only 8.3% was improved at 3rd weeks and this was increased to 25% at the end of 6 weeks treatment, but the difference was not significant (Table **3**).

In severe active group there was improvement in clinical state at 3rd weeks of treatment which was accounted for 58.3%. This improvement was increased to 83.4% at 6 weeks which was significant (P=0.009) as compared with severe control group which had improvement of 11.1% at 3rd weeks and that was increased to 22.2% at the end of 6 weeks of treatment period (Table **3**).

The total active group showed much significant improvement at 3rd week and 6th week of treatment (P=0.000) as compared with control group. The frequency of improvement rate was 68.4% at 3rd weeks of treatment period which was increased to 92.1% at the 6th week of treatment. However, the control group showed 13.3% rate of improvement at 3 weeks and was increased to 30.1% at 6th week of treatment.

Tolerability to the Exacerbating Factors

The tolerability to allergen exposure was improved in the active group (44.7%) as compared to control group (10%) at the end of 3rd week (P=0.002) of treatment. Responses to temperature variation showed improvement in active group (18.4%), while in control group it was found to be 6.6%, the difference was found to be not significant (Table **2**). Another environmental factor that showed improvement was smoking and irritant which accounted for 10.5% in active group at the end of 3 weeks of treatment, while the corresponding value in control group was 3.3%, however this difference was also not found to be significant.

Table 3. Symptomatic response after 6 weeks nasal treatment.

Group		Active Group				Control Group			
		0w	3w	6w	P value	0w	3w	6w	P value
Mild	Symptomatic	10 (100%)	2 (20%)	0 (0%)		9 (100%)	7 (77.7%)	5 (55.5%)	
	Symptom free	0	8 (80%)	10 (100%)	0.000	0	2 (22.2%)	4 (44.4%)	NS
Moderate	Symptomatic	16 (100%)	5 (31.2%)	1 (6.2)		12 (100%)	11 (91.6%)	9 (75%)	
	Improved	0	3 (18.7%)	4 (25%)		0	1 (8.3%)	2 (16.6%)	
	Symptom free	0	8 (50%)	11 (68.7%)	0.000	0	0	1 (8.3%)	NS
Severe	Symptomatic	12 (100%	5 (41.6%)	2 (16.6)		9 (100%)	8 (88.8%)	7 (77.7%)	
	Improved	0	4 (33.3%)	3 (25%)		0	1 (11.1)	1 (11.1%)	
	Symptom free	0	3 (25%)	7 (58.3%)	0.005	0	0	1 (11.1%)	NS
Total	Improved and symptom free	0	26 (68.4%)	35 (92.1%)		0	4 (13.3)	9 (30.1%)	

Active versus control	Mild	Moderate	Severe	Total
3 weeks	0.01	0.008	0.02	0.000
6 weeks	0.01	0.002	0.009	0.000

At the end of 6 weeks of treatment with topical use, the improvement in tolerability of allergen exposure in active group became 55.2% which is significant (P=0.006) as compared with the control group which accounted for 20% at the same time. Responses to temperature variations and irritants were improved but without significant differences between active and control groups. Table **2**.

Strength of NS Oil Treatment via Both Systemic & Topical Use on Allergic Rhinitis

The most affected symptom by treatment was rhinorrhoea, followed by nasal itching, sneezing, nasal congestion and improvement of sleep. All these effects were better in topical NS oil treatment with the exception of conjunctivitis which was only affected by systemic treatment (Table **4**).

Side Effects

The only side effect of systemic NS oil topical treatment was reported as nasal dryness (17.8%) in the active treatment group, (Table **5**).

Comparison between Both Routes Treatment

Topical use was more effective, less costly, earlier response to treatment and with fewer side effects than the systemic use (Table **6**).

DISCUSSION

In a previously reported study [28], systemic use of black seed oil was effective in the treatment of AR. The current study indicated that 96.7% of mild active group became symptoms free at the end of 6 weeks while 47.7% were improved. In addition, in the moderate group, 31.8% of patients became symptom free and 37% showed improved in their symptoms, while in severe group, 22.2% became symptom free after 6 weeks of treatment period. Thus the complete improvement (symptoms free period) was estimated to be approximately four times lower? in the mild group and double as compared to severe group. The improvement in mild and moderate active group was highly significant (P<0.01) as compared to control group, while in severe group, in spite of good clinical improvement, there was no significant difference as compared to control group. Associated allergic symptoms such as conjunctivitis, asthma and urticaria also showed improvement in active groups, furthermore the effect on total serum IgE level was also found to be significant. However, treatment cessation resulted in high rate of recurrence. The reappearance of symptoms was reported more in mild group as compared to moderate and severe group. This variation was a reflection of the better response to treatment in mild as compared to other two groups. Thus the response to treatment with black seed oil was severity driven [28].

The topical use of black seed oil as nasal drop was more effective with better clinical improvement than the systemic use which may be due to the fact that more concentrated drugs will be available to the nasal mucosa. In addition, topical use was also effective in induction of good tolerability to the exacerbating factors after 6 weeks of treatment with black seed oil. However, the tolerability of exacerbating factors was influenced by factor type. Topical application of oil was also found to be more effective than systemic use in ameliorating exacerbating factors effect which may be due to higher antihistamine membrane stabilizing action of NS than in systemic route. Furthermore, this may be a result of its potent inhibitory effect on leukotirens release [34-36].

The side effects of *N. sativa* extract used in allergic rhinitis was considered minor as compared with conventional drugs used for allergic rhinitis like steroids or antihistamines. One of these side effects of systemic *N. sativa* use was mild diarrhea which did not affect the administration of the herb. Excessive nasal dryness was much more in topical use and

Table 4. Effect of *N. sativa* oil treatment *via* both systemic and topical use on allergic rhinitis symptoms.

Variable	Percent Improvement Systemic Use	Percent Improvement Topical Use
Rhinorrhoea	80.4	100
Sneezing	79.4	89.7
Nasal itching	78.4	90.0
Nasal obstruction	50.9	73.5
Conjunctivitis	60.8	0
Sleep improvement	50.0	73.5
Smell sense improvement	21.5	39.7

Table 5. Side effects of black seed oil after topical applications.

Side Effects	Time of Occurrence	No. of Patients	% From Total Active Group
Excessive nasal dryness	5-12 days of use	5	17.8%

Table 6. Comparison between systemic and nasal NS extract use in AR.

No.	Subject	Systemic Use	Topical Nasal Use
1	Cost	More	Less
2	Patient tolerance	Better	Less especially by children
3	Effects on symptoms of AR	Effective	More effective
4	Side effects	-Diarrhea+++ -Nasal dryness+	Nasal dryness+++
5	Effect on associated diseases	Effective	Not effective
6	Effect on nasal symptoms exacerbating factors	Mild –moderate effect	More effect with better in tolerability to the exacerbating factors
7	Effect on hyposmia	Mild effect	Better effect
8	Beginning of the effect	5^{th} -7^{th} day (later than local use)	2^{nd} -3^{rd} day (earlier than systemic use)

this may be due to more potent anti cholinergic effect in topical use than systemic use [34-36].

The local use has more therapeutic effect on AR symptom. Local use leads to more effect on the sense of smell than systemic use. This is because of the olfactory disturbances which may reflect the extent of mucosal disease within the nasal cavity, particularly within the upper part of the nose [37]. The mechanism of *N. sativa* which was responsible to the improvement of hyposmia and sense of smell was based on its ability to decrease mediator release with its anti-inflammatory properties. This appears to decrease mucosal edema and inflammation leading to the improvement in sense of smell in some hyposmia patients. This was more in topical use because nasal mucosa was affected directly by obvious concentrated drug. It was also showed in systemic use though to a less degree. Systemic side effects were lower in local use because of the low dose used while local side effect (excessive nasal dryness) was more in local use.

CONCLUSIONS

It was concluded that topical application of *N. sativa* oil is an effective treatment modality for allergic rhinitis. The topical application of oil was to found to be more effective than oral administration, and less expensive with fewer side effects.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

PATIENT CONSENT

Declared none.

ABBREVIATIONS

AOAC = Association of Analytical Chemistry

AR = Allergic rhinitis

FEV1 = Forced expiratory volume in first second

HDM = House dust mite

INSs = Intranasal steroids

NS = *Nigella sativa*

PAR = Perennial allergic rhinitis

SAR = Seasonal allergic rhinitis

SIT = Specific immunotherapy.

TTH = Tikrit Teaching Hospital

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Received: April 23, 2012 Revised: June 29, 2013 Accepted: July 07, 2013