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## ORIGINAL STUDY

# Comparative Study Between the Efficacy of Azelastine–Fluticasone Nasal Spray Combination and Fluticasone Nasal Spray Combined With Oral Cetirizine in Allergic Rhinitis

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## Abstract

**Aim:** The aim of the study was to compare between administering intranasal AZE/FLU combination, and the conventionally used oral Cetirizine with intranasal Fluticasone for Allergic Rhinitis. **Methods:** A prospective, randomized, controlled study, where 100 patients were enrolled into two groups: Group A patients received AZE/FLU twice daily, while Group B patients received fluticasone propionate once daily in the morning and oral Cetirizine at night. Patients recorded nasal and ocular symptom scores daily in a diary using a clear Arabic printout of VAS scores. Pre-treatment and posttreatment scores were collected at regular visits. **Results:** Regarding the progression of symptoms through checkpoints over the trial time; on days 7, 14, and 21 (trial end), the calculated average VAS scores proved no statistically significant difference when comparing the results of both groups. Comparing the collected data at day 7 showed no statistically significant difference between either of the studied groups, denoting that neither of the studied approaches provided significant improvement in quality of life over the other regarding timely symptom control. **Conclusion:** Although no significant difference was noted between the two approaches regarding adequate symptom control by the end of the first week from trial initiation (denoted by achieving VAS <5/10, signaling improved quality of life), 42% of patients enrolled in the study group A reported VAS <5/10 within 7 days of treatment, compared with 32% of patients from the control group B. This proposes that even a nonsignificant statistical difference cannot contradict a satisfactory real-life noted clinical finding suggesting a clinical preference for a treatment approach that would provide better compliance.

**Keywords:** Allergic rhinitis, Azelastine, Cetirizine, Fluticasone, Azelastine hydrochloride/fluticasone propionate, Intra-nasal antihistamines, Intranasal steroids, Oral antihistamines, VAS scale

## 1. Introduction

Allergic rhinitis (AR) is a very common disease affecting children and adults globally and is the most widespread noninfectious rhinitis type. This inflammatory condition of the nasal mucosa is triggered by an interaction between environmental allergens and specific immunoglobulin E in sensitized patients [1].

However, current treatments often fail to provide sufficient control. In clinical trials and real-life studies many patients experience inadequate symptom relief on taking intranasal corticosteroids (INCS) due to their slow onset of action, symptom breakthrough, and an efficacy ceiling of 60% reduction from baseline in reflective total nasal symptom score (rTNSS), leading to patient dissatisfaction and poor compliance [2].

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**Abbreviations:** AR, Allergic Rhinitis; AZE/FLU, Azelastine hydrochloride/Fluticasone propionate; INCS, Intranasal corticosteroids; rTNSS, reflective total nasal symptom score; ARIA, Allergic Rhinitis and its Impact on Asthma; VAS, Visual Analog Scale

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## 2. Background

Although AR is not a life-threatening condition, it can have a substantial socioeconomic impact and negatively affect the quality of life. By limiting daily activity, AR may have a detrimental impact on social behavior and the emotional well-being of children and may be responsible for absenteeism and inefficient educational performance. The direct economic cost can also be fairly high, and this is of particular importance in under-resourced countries and economically disadvantaged populations [3].

The management of AR could be divided into removal or avoidance of allergens, pharmaceutical treatment, immunotherapy, and surgical intervention. Among these, pharmaceutical treatments using antihistamines, leukotriene receptor antagonists, topical steroids, vasoconstrictors, etc. play an important role in improving and maintaining the quality of life. In particular, antihistamines (oral, eye drop, and nasal drop formulations) are widely indicated for mild to severe conditions [4].

INCS are the first-line therapy for moderate-to-severe AR and are the most effective medication for controlling AR symptoms. INCS exhibit potent anti-inflammatory action due to the effects on several cell types, including topically on the nasal mucosa. They hinder the release of inflammatory mediators and cytokines, thereby reducing nasal mucosal inflammation. They provide symptomatic and effective relief when used on a regular basis or as needed. However, they are most effective when used regularly, reaching maximum benefit within 2 weeks [5].

Of the known histamine receptors (H1, H2, H3, and H4), primarily H1 receptors are responsible for immediate-type allergic reactions. Thus, it is predominantly H1-antihistamines that are used in the treatment of AR. While first-generation H1-antihistamines (e.g., clemastine, meclizine) have potent sedative effects, second-generation antihistamines (e.g., azelastine, cetirizine, loratadine, desloratadine, fexofenadine, levocetirizine) have only mild or no sedating characteristics and should thus be preferred to first-generation agents. These antihistamines are used systemically or sometimes also topically and are given one to two times per day [6].

A combination of intranasal antihistamine and corticosteroid spray represents an alternative therapeutic option for the management of AR. One such formulation is currently available for intranasal use as a combination of azelastine hydrochloride and fluticasone propionate (AzeFlu). This agent is also designated in the literature as MP-AzeFlu or MP29-02 and was originally introduced in the United

States under the trade name Dymista (Meda Pharmaceuticals, Somerset, New Jersey) [7].

One meta-analysis looked into the role of intranasal corticosteroids in patients with allergic rhinitis ( $n = 2267$ ) and showed that it provides significantly greater relief of nasal congestion than oral antihistamines. It is, however, a combination therapy that has proven to not only improve symptomatology but also be found to be more convenient and effective [8].

This trial aims to study the efficacy of implementing the use of intranasal Azelastine hydrochloride/Fluticasone propionate combination in the nasal spray pharmaceutical formulation, compared with the conventionally used oral selective H1-receptor blocker (Cetirizine) and intranasal corticosteroid (Fluticasone propionate) as a treatment approach for patients with AR.

## 3. Patients and methods

This prospective, randomized, controlled study was performed in Benha University Hospital and Gamal Abdel Nasser Health Insurance Hospital in Alexandria and involved outpatients frequenting the otorhinolaryngology departments of both hospitals over 6 months from July to December, 2020. The study was approved by the hospitals' Ethics Committee, meeting the criteria of the Helsinki Declaration, and following informed consents of the patients themselves or their first-degree relatives.

### 3.1. Patients

Eligibility requirements were as follows: Subjects aged 18–65 years, with a minimum 2-year history of moderate-to-severe AR according to the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria for moderate-to-severe AR [9]. All subjects were requested to stop anti-allergic treatment 3 days before inclusion in the study (washout period). Included patients received a printout of the visual analog scale (VAS) [10].

### 3.2. Methods

One hundred patients selected from those frequenting the hospital's ORL department and meeting the previously stated inclusion criteria were enrolled in the trial according to the sample size calculation formula.

The study comprised a 3-days washout period with cessation of all sorts of previously prescribed medication, and a 21-day treatment period, with study visits at randomization (day 1) and at the end

of the trial (day 21). The patients were treated with either Azelastine hydrochloride/Fluticasone propionate nasal spray or Fluticasone propionate nasal spray and Cetirizine oral tablet.

Patients recorded nasal and ocular symptom scores once daily in a diary using the VAS score after receiving a printout translated into Arabic with a clear explanation. The pretreatment and post-treatment scores were collected at the visits.

The included patients were randomly divided into two groups using their medical record number (MRN) such that the patients with even MRNs, who were managed by Azelastine hydrochloride/Fluticasone propionate nasal spray were enrolled in the study group (Group A), and patients with odd MRNs, who were managed by Fluticasone propionate nasal spray and Cetirizine oral tablet were enrolled into the control group (Group B).

#### Group A: the study group

The 50 random patients enrolled in Group A received treatment in the following manner:

**Azelastine hydrochloride/Fluticasone propionate** (125/50  $\mu\text{g}$  AZE/FP per spray) administered as one spray/nostril twice daily, separated by approximately 12 h (total daily dose: AZE, 500  $\mu\text{g}$ ; FP, 200  $\mu\text{g}$ ).

#### Group B: the control group

However, the 50 random patients enrolled in Group B received the following management:

**Fluticasone propionate** (50  $\mu\text{g}$  per spray) administered as two sprays/nostril once daily in the morning (total daily dose: 200  $\mu\text{g}$ ).

#### PLUS Cetirizine

oral tablet (10 mg) administered as one tablet at night.

### 3.3. Implementing the use of VAS during the trial

Considering the fact that symptoms of allergic rhinitis are often subjective, and difficult to assess and verify, individualized therapy and continuous monitoring of the disease create the need for a simple and effective tool. VAS is an instrument that can be used in daily practice. VAS is usually a horizontal 100 mm–long scale with two opposing descriptors at its endpoints. Patients with allergic rhinitis specify a point on the scale that best corresponds to the severity of their symptoms. Symptoms of allergic rhinitis can be assessed globally or separately on different scales (nasal obstruction, rhinorrhea, itching, sneezing) in addition to ocular symptoms (Fig. 1).

It has been shown that irrespective of a baseline VAS score, a 23 mm improvement indicates that treatment has been effective, while a 30 mm improvement is associated with an improvement in the quality of life parameters.

The scale is particularly useful for documentation of allergic rhinitis severity and disease control in everyday practice due to its simplicity, time effectiveness, and low susceptibility to errors [10].

VAS was implemented as the main tool for the assessment of the progress of symptoms daily by the patient as a monitor for response experienced to the treatment program administered to each patient assigned to either of the two groups.

VAS provided a means to convert rather a subjective view of symptom progression to objective data that could be collected and tabulated to be analyzed statistically.

The scale was carefully explained to each patient, and they received a printout of the scale translated

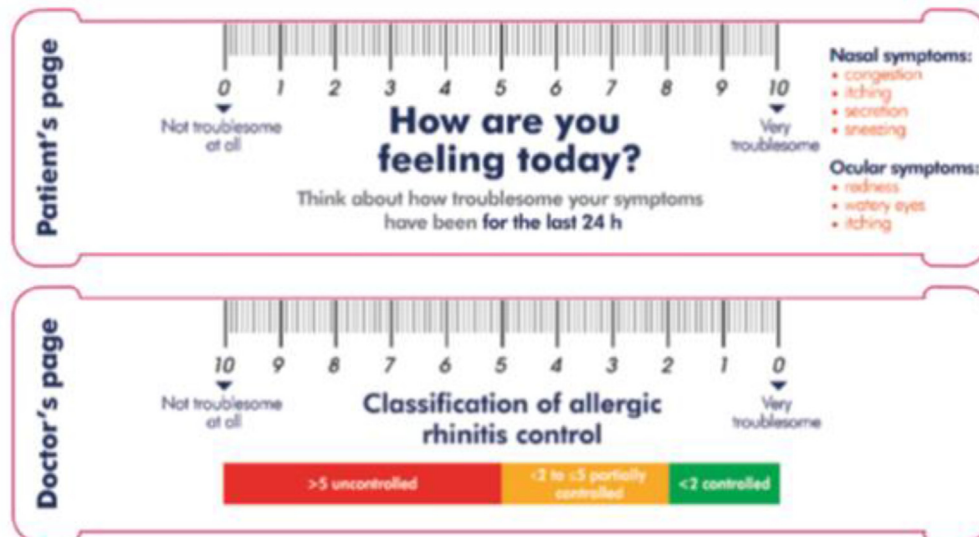


Fig. 1. VAS (SYBILSKKI AJ, 2018 [10]).

into Arabic language with clear instructions to record symptom severity, either nasal or ocular symptoms, on a daily basis to be reviewed at the end of the trial visit on day 21, and to be compared with the initial score recorded at the randomization visit on day 1.

### 3.4. Data collection

Data were recorded and compared at two stages throughout the study; the first stage entailed recordings of the baseline criteria of all patients before beginning the trial, and data were recorded for each patient enrolled in either of the two groups at randomization (day 1). The baseline criteria included descriptive data, namely age, gender, and course of moderate-to-severe AR in years. Basic AR symptoms at randomization were divided into two categories, nasal and ocular symptoms, and baseline symptom severity was determined according to the VAS scoring.

The second stage of data collection was specified to monitor the outcome of the study, where two outcome categories were monitored; primary outcome was the assessment of global symptoms progression (nasal and ocular) in relation to time, through recording the average VAS (VAS/10) calculated from each patient's assessment at weekly intervals (day 7 and day 14) and at the end of trial (day 21) regarding either of the two patient groups, and secondary outcome which entailed recording if both of the two symptom categories (nasal or ocular), either, or none, had shown adequate improvement up to VAS <5/10, indicating improved quality of life, recorded as either 2, 1, or 0, within the first week (day 7) of the start of trial.

## 4. Results

Throughout the study period, a total of 100 patients of those frequenting the Hospital's ORL Department were involved in the study, following the implementation of the aforementioned inclusion and exclusion criteria. Patients enrolled into Group A (the study group) were those who would be managed by Azelastine hydrochloride/Fluticasone propionate nasal spray, while patients enrolled in Group B (the control group) were those who would be managed by Fluticasone propionate nasal spray and Cetirizine oral tablet.

### 4.1. Stage 1: baseline criteria

#### 4.1.1. Descriptive data

Baseline characteristics, namely age, gender, and course of moderate-to-severe allergic rhinitis (AR)

were recorded for each patient enrolled into either of the two groups at randomization.

Table 1 shows the baseline characteristics of patients enrolled into either of the two groups before initiation of the study.

Both groups were nearly homogeneously distributed as regards demographic data.

There were no statistically significant differences between both groups regarding individual items; namely age and gender ( $P > 0.05$ ).

As regards the course of moderate-to-severe AR in years for patients enrolled in both groups, the recorded data showed no statistically significant difference between both groups ( $P > 0.05$ ).

Table 2 shows the recorded data of the course of AR in years for all patients.

#### 4.1.2. Nasal and ocular symptom score using the VAS

VAS was used at the randomization visit to determine in an objective rather than a subjective manner the severity of symptoms of AR, where patients were instructed to specify a point on the scale that best corresponds to the severity of their symptoms. Symptoms of allergic rhinitis were assessed separately on different scales (nasal obstruction, rhinorrhoea, itching, sneezing) in addition to ocular symptoms.

Values collected, tabulated, and analyzed for VAS scores of patients from both groups as regards their nasal and ocular symptoms at randomization showed globally homogeneous results with no statistically significant differences.

Table 1. Comparison between the two studied groups according to demographic data.

	Group A (n = 50)	Group B (n = 50)	P
	Number (%)	Number (%)	
Sex			
Male	26 (52.0)	23 (46.0)	0.548
Female	24 (48.0)	27 (54.0)	
Age (years)			
Min.–Max.	18.0–64.0	18.0–64.0	0.949
Mean ± SD.	40.54 ± 14.27	40.36 ± 13.83	

\*SD: Standard deviation.

†P: P value for comparing the two studied groups.

Table 2. Comparison of the two groups according to the course of moderate-to-severe AR.

Course of AR (years)	Group A (n = 50)	Group B (n = 50)	P
Min–max	3.0–19.0	3.0–19.0	0.948
Mean ± SD	10.88 ± 4.79	10.92 ± 4.79	

\*SD: Standard deviation.

†P: P value for comparing between the two studied groups.

Data analysis of scores obtained from the VAS scale as specified by the patients regarding the severity of nasal symptoms represented no statistically significant difference worth mentioning between the two groups ( $P > 0.05$ ). Furthermore, statistical analysis of data obtained from the patients' VAS score regarding the mentioned ocular symptoms of AR, namely redness, tearing, and itching also showed no statistically significant difference ( $P > 0.05$ ).

Table 3 represents the statistical analysis of comparable data between both of the studied groups regarding nasal symptoms obtained through VAS, while Table 4 represents the analysis of VAS scores showing the severity of ocular symptoms.

## 4.2. Stage 2: outcome

### 4.2.1. Primary outcome

Determining the primary outcome was achieved through assessment of global symptoms progression (nasal and ocular) in relation to time, through recording the average VAS (VAS/10) calculated from each patient's assessment at weekly intervals (day 7 and day 14) and at the end of the trial (day 21) regarding either of the two patient groups. This record was obtained through the collection of data recorded by the patients themselves through their daily assessment of their symptom severity from each patient's individual VAS. The progressive records of each of the examined nasal symptoms (obstruction, itching, rhinorrhea, and sneezing) were converged into an average VAS score reflecting nasal symptom progression. Similarly, the recorded data for the progress of each of the ocular symptoms (redness, tearing, and

Table 3. Comparison between the two groups according to nasal symptoms score using VAS.

Nasal symptoms Score via VAS	Group A (n = 50)	Group B (n = 50)	P
<b>Nasal Obstruction</b>			
Min–max	7.0–10.0	7.0–10.0	0.931
Mean $\pm$ SD	8.30 $\pm$ 1.15	8.28 $\pm$ 1.14	
<b>Itching</b>			
Min–max	6.0–10.0	6.0–10.0	0.753
Mean $\pm$ SD	8.24 $\pm$ 1.25	8.16 $\pm$ 1.28	
<b>Rhinorrhea</b>			
Min–max	6.0–10.0	6.0–10.0	0.806
Mean $\pm$ SD	8.42 $\pm$ 1.21	8.36 $\pm$ 1.22	
<b>Sneezing</b>			
Min–max	6.0–10.0	6.0–10.0	1.000
Mean $\pm$ SD	8.16 $\pm$ 1.27	8.16 $\pm$ 1.25	
<b>Average</b>			
Min – Max	6.5–10.0	6.5–10.0	0.823
Mean $\pm$ SD	8.29 $\pm$ 0.88	8.25 $\pm$ 0.90	

\*SD: Standard deviation.

†P: P value for comparing between the two studied groups.

Table 4. Comparison between the two groups according to ocular symptoms score using VAS.

Ocular symptoms score via VAS	Group A (n = 50)	Group B (n = 50)	P
<b>Redness</b>			
Min–max	6.0–10.0	6.0–10.0	0.938
Mean $\pm$ SD	8.14 $\pm$ 1.29	8.16 $\pm$ 1.28	
<b>Tearing</b>			
Min–max	6.0–10.0	6.0–10.0	0.943
Mean $\pm$ SD	8.02 $\pm$ 1.38	8.0 $\pm$ 1.40	
<b>Itching</b>			
Min–max	6.0–10.0	6.0–10.0	0.945
Mean $\pm$ SD	8.0 $\pm$ 1.44	8.02 $\pm$ 1.44	
<b>Average</b>			
Min–max	6.0–10.0	6.0–10.0	0.981
Mean $\pm$ SD	8.05 $\pm$ 1.25	8.06 $\pm$ 1.25	

\*SD: Standard deviation.

†P: P value for comparing between the two studied groups.

itching) was converted into an average VAS score reflecting the ocular symptom progression. Both values were chronologically recorded and compared to represent the global progress of symptoms over the weekly checkpoints till the end of the trial.

As regards the progression of nasal symptoms through the weekly checkpoints over the time of the trial, on day 7, 14, and 21 (which marks the end of the trial), the calculated average VAS scores proved no statistically significant difference when comparing the results of both groups, at either of the marked checkpoints ( $P > 0.05$ ).

Similarly, while examining the progression of ocular symptoms through the weekly checkpoints over the time of the trial, the calculated average VAS scores showed no statistically significant difference when comparing the results of both groups, at either of the marked checkpoints ( $P > 0.05$ ).

Table 5 represents the comparison between average VAS scores calculated on days 7, 14, and 21 for patients from both groups, denoting the progress of nasal symptoms of AR.

Table 6 represents the comparison between average VAS scores calculated on days 7, 14, and 21 for patients from both groups, denoting the progress of ocular symptoms of AR.

### 4.2.2. Secondary outcome

It is considered imperative that the time frame till achieving adequate control of nasal and ocular symptoms of AR would represent a key element in the assessment of improvement of quality of life for the patient.

Therefore, the secondary outcome of our study was concerned with determining whether any of the studied treatment approaches would provide adequate control of any of the symptom categories for AR by the end of the first week from the

Table 5. Comparison between the two studied groups according to nasal symptoms progression (primary outcome) using VAS.

Average nasal symptoms VAS	Group A (n = 50)	Group B (n = 50)	P
<b>Day 7</b>			
Min–max	3.50–7.0	3.0–7.10	0.548
Mean ± SD	4.99 ± 0.87	5.10 ± 1.02	
<b>Day 14</b>			
Min–max	1.0–4.0	1.0–3.80	0.455
Mean ± SD.	2.36 ± 0.72	2.25 ± 0.74	
<b>Day 21</b>			
Min–max	1.0–2.0	1.0–2.0	0.975
Mean ± SD	1.28 ± 0.31	1.28 ± 0.32	

\*SD: Standard deviation.

†P: P value for comparing the two studied groups.

Table 6. Comparison of the two studied groups according to ocular symptoms progression (primary outcome) using VAS.

Average ocular symptoms VAS	Group A (n = 50)	Group B (n = 50)	P
<b>Day 7</b>			
Min–Max	3.0–7.20	2.0–7.50	0.697
Mean ± SD	4.74 ± 1.06	4.83 ± 1.23	
<b>Day 14</b>			
Min–Max	1.0–3.70	1.0–3.30	0.068
Mean ± SD	2.04 ± 0.64	1.81 ± 0.61	
<b>Day 21</b>			
Min–max.	1.0–2.0	1.0–1.80	0.276
Mean ± SD	1.22 ± 0.31	1.16 ± 0.23	

\*SD: Standard deviation.

†P: P value for comparing the two studied groups.

initiation of the trial. This was achieved by recording if both of the two symptoms categories (nasal or ocular), either, or none, had shown adequate improvement up to VAS <5/10, indicating improved quality of life, recorded as either 2, 1, or 0, within the first week (day 7) of the start of trial.

By examining and comparing the collected data at day 7 of the start of the trial, again, there has been no statistically significant difference proven between both the studied patient groups ( $P > 0.05$ ), denoting that none of the studied treatment approaches provided significant improvement of the quality of life over the other approach regarding timely control of symptoms (Table 7).

Table 7. Comparison between the two studied groups according to ocular/nasal symptoms adequate improvement on day 7 (secondary outcome).

Ocular/Nasal symptoms adequate improvement on day 7	Group A (n = 50) Number (%)	Group B (n = 50) Number (%)	P
0	15 (30.0)	24 (48.0)	0.181
1	14 (28.0)	10 (20.0)	
2	21 (42.0)	16 (32.0)	

\*P: P value for comparing the two studied groups.

## 5. Discussion

Allergic rhinitis is a chronic upper airway disease of increasing prevalence and remains a significant health-care problem. The condition can have a major detrimental impact on the quality of life and social productivity.

Clinical practice guidelines for the management of AR recommend imperative goals, including the prevention of allergies, reduction in allergen exposure, and effective pharmacological management [11]. The most widely used and effective medications to manage allergic rhinitis are oral or topical antihistamines and topical nasal steroids. These medications aim to achieve improved symptom control and are not a cure for allergies. They need to be taken for as long as there is allergen exposure resulting in symptoms [12]. Fluticasone propionate is a topically active corticosteroid with low systemic bioavailability attributed to massive hepatic first-pass metabolism. Azelastine nasal spray is a topically administered second-generation antihistamine and selectively antagonizes the H1-receptor. It has one of the most rapid onsets of action (15 min with nasal spray) among the currently available rhinitis medications, and its effect lasts at least 12 h, thus allowing for a once or twice-daily dosing regimen [13].

It is often asked whether there are clinically significant differences between the antihistamines available for the treatment of allergic rhinitis. Both intranasal and oral second-generation antihistamines are recommended as first-line therapy for allergic rhinitis; however, earlier well-controlled comparative clinical trials of 2 weeks of treatment with oral second-generation antihistamines have primarily shown similarities among them [14].

Although azelastine nasal spray significantly improved symptoms in patients who remained symptomatic even after treatment with oral loratadine or fexofenadine compared with placebo ( $P \leq 0.007$ ), these studies did not directly compare active-treatment groups. The present study, therefore, was designed with a fairly sufficient sample size to detect significant differences in the selected efficacy parameters between Azelastine hydrochloride/Fluticasone propionate combination in the nasal spray pharmaceutical formulation, compared with the conventionally used oral selective H1-receptor blockers (Cetirizine), along with intranasal corticosteroids (Fluticasone propionate). The study population included a sufficiently representative and homogeneous sample of patients with symptoms of AR caused by a broad spectrum of seasonal allergens.

Regarding the demographic characteristics of the study population, selected cases of allergic rhinitis

were homogeneously distributed among a wide array of age groups ranging from 18 to 64, with a mean age of 40 years. This is contrasting with a study by Bhadouriya et al., in which most cases were in the age group of 21–30 years with a mean age of 31.5 years [15].

There were 24 females in group A as compared with 27 females in group B in the study. The gender distribution difference was not significant. This is comparable to the study by Dalvi and Havle et al. [16]. The presentation and clinical course of AR do not differ per se between males and females.

In almost all cases the four main nasal symptoms were present before therapy: sneezing, nasal obstruction, nasal discharge, and nasal itching, along with the well-known ocular symptoms (redness, tearing, and itching) and they were all deemed 'quite bothersome' by the patients.

In the prospective study conducted by Dhanush H.C., out of 80 patients, 40 were treated with topical fluticasone propionate (50 mcg) and azelastine (140 mcg), and 40 patients were treated with fluticasone propionate (50 mcg) only. All participants of both groups were assessed before and after the treatment on a four-point symptom scale (zero to three) for the nasal symptoms category. In this study, the fluticasone propionate-alone group was also effective in reducing symptoms of AR. The difference in reduced symptoms score between the two patient groups was statistically significant indicating that fluticasone propionate and azelastine nasal spray is more effective in reducing symptoms of AR than fluticasone propionate alone. The fluticasone propionate with the azelastine group also had a significantly greater reduction in individual symptoms of nasal obstruction, nasal discharge, and nasal itching [11].

In contrast to the study conducted by Dhanush H.C. et al., our current study utilized oral selective H1-receptor blockers (Cetirizine) combined with topical fluticasone propionate as the treatment approach for the control group patients, and this resulted in a nonsignificant statistical difference between the two approaches as regards the comparison between average VAS scores calculated on days 7, 14 and 21 for patients from both groups, denoting progress of nasal symptoms of AR. These findings highlight the importance of including selective non-sedating H1-antihistamines in the management protocol of AR, regardless of the route of administration. Nevertheless, a satisfactory response to two agents administered in two separate pharmaceutical forms must bring into consideration the superiority of utilization of a combination form containing both agents in a single pharmaceutical

formulation, preferably a topical one that would promote patients' compliance.

Another study by Jonathan C. et al. compared the efficacy and tolerability of azelastine nasal spray administered at the recommended dosage with those of cetirizine in the treatment of moderate-to-severe SAR. This randomized, double-blinded, parallel-group, 2-week comparative study was conducted in patients with moderate-to-severe SAR. Patients were randomized to receive azelastine nasal spray two sprays per nostril twice daily plus placebo tablets or cetirizine 10-mg tablets once daily plus a placebo saline nasal spray for the 2-week double-blind treatment period. The primary efficacy variables were (1) change from baseline to day 14 in the 12-h reflective total nasal symptom score (TNSS), which combines scores for rhinorrhea, sneezing, itchy nose, and nasal congestion, and (2) onset of action, based on the instantaneous TNSS over 4 h after the first dose of the study drug. Over 2 weeks of treatment, both groups had significant improvements in the TNSS compared with the baseline ( $P < 0.001$ ). The overall change in TNSS was significantly greater with azelastine nasal spray compared with cetirizine. In terms of onset of action, azelastine nasal spray significantly improved the instantaneous TNSS compared with cetirizine at 60 and 240 min after the initial dose [17].

The previous study results collected by Johnathan C. et al. support the treatment approach proposed by our study. Again, even though no statistically significant difference was proven by the data analysis of our results regarding the two treatment approaches, the proven higher efficacy and tolerability besides the more rapid onset of action of topical Azelastine hydrochloride as a nasal spray over oral Cetirizine in global symptoms control provides solid ground for the preference of a topical pharmaceutical form containing Azelastine hydrochloride/Fluticasone propionate combination over the use of nasal Fluticasone propionate plus oral Cetirizine, regarding the established rapid onset of action and the opportunity for better patient compliance.

The therapeutic efficacy of any new treatment must be demonstrated in randomized placebo-controlled trials, yet the rigid admission rules to trials often result in treatment populations quite different from those seen in daily outpatient medical practice [18]. Therefore, real-life studies expand the observations and highlight issues not addressed in trials. The efficacy of Azelastine hydrochloride/Fluticasone propionate combination in routine clinical practice was evaluated in a 2-week, prospective, observational study in patients aged  $\geq 12$  years. The



study population included 1781 patients with moderate-to-severe AR for whom monotherapy with either intranasal H1- antihistamines or intranasal corticosteroids had been considered insufficient, who had been prescribed the drug at standard doses. Patients scored their symptoms by a visual analog scale from 0 mm (not at all bothersome) to 100 mm (very bothersome) before starting treatment, on days 1, 3, and 7 after treatment initiation and treatment end. The perceived level of disease control was also assessed by patients on day 3. Azelastine hydrochloride/Fluticasone propionate combination provided satisfactory symptom control from day 1, as measured by a 21.3 mm visual analog scale decreased by treatment end and by a perception of disease control in 50% of patients after just 3 days of treatment [6].

Our present study utilized a research approach similar to the aforementioned study by Klimek et al., where the VAS score was used to assess the subjective perception of disease symptom control by the patient, while comparing Azelastine hydrochloride/Fluticasone propionate to the commercially available and well-known oral selective H1-receptor blockers (Cetirizine), along with intranasal corticosteroids (Fluticasone propionate). Although no statistically significant difference was noted between the two treatment approaches regarding the timely adequate control of symptoms by the end of the first week from trial initiation (denoted by achieving VAS <5/10 signaling improved quality of life), we found that 42% of patients enrolled to group A (the study group) reported VAS <5/10 within 7 days of treatment, compared with 32% of patients belonging to the control group B reporting similar improvement. This proposes that even a nonsignificant statistical difference cannot contradict a satisfactory real-life noted clinical finding suggesting a clinical preference to a treatment approach over the other.

### 5.1. Conclusion

Azelastine hydrochloride/fluticasone propionate is a combination of two drugs—a second-generation antihistamine and an intranasal corticosteroid—that are mainstays of AR therapy, but its efficacy was shown to be more clinically, rather than statistically, satisfactory than that of the two agents administered separately. This responds to the call of AR patients for new therapies that achieve a more rapid and substantial relief of symptoms and gives a better chance for improved patient compliance. It also paves the way for the development of other combinations of intranasal

corticosteroids and antihistamines as has occurred in the past for the treatment of asthma, with combinations of inhaled corticosteroids and  $\beta$ 2-agonists, allowing physicians to make the most appropriate decision for individual patients.

### 5.2. Limitations of the study

Several limitations of this study must be taken into account. First, as the VAS scoring system was used as a means for the assessment of symptom severity and progression, it is a tool depending mainly on the subjective assessment of the patient that might not be completely accurate, therefore the obtained results cannot be confidently dependable while lacking a solid objective test for clinical judgment. Second, patients were monitored only during the duration of the trial, and no data were collected on a long-term basis for proper assessment of the condition over seasonal variations of symptom severity and control. Finally, the sample size was rather small in comparison to previous studies examining the same topic over a larger scale of subjects.

### Authors contributions

*Irinie Georges M. Soliman* acquired, analyzed, and interpreted the patient data by conducting the randomization as well as the weekly follow-up patients' visits. *Ahmed Ashraf S. Elhamshary* devised the study design and methodology and supervised the analysis of findings and results and gave final approval of the version to be published. *Mostafa Gomaa S. El Shahat* drafted the article and reviewed the study progress critically for important intellectual content and provided instructions about data collection and analysis. All authors read and approved the final manuscript, and each author believes that the manuscript represents honest work.

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### Key messages

Allergic rhinitis is a common disease, affecting children and adults, and is the most widespread type of noninfectious rhinitis. Current treatments for AR provide insufficient control for many patients. A combination of intranasal antihistamine and corticosteroid spray represents an alternative therapy. One such formulation is available for intranasal use as a combination of azelastine hydrochloride/fluticasone propionate (AZE/FLU).

## Criteria for inclusion of the authors

Authorship credit was based on substantial contributions to each of the three components mentioned below: (1) concept and design of study or acquisition of data or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

## Ethical approval and consent to participate

The study was approved by the Research Ethics Committee, Benha Faculty of Medicine (REC-FOMBU), and was performed in accordance with the ethical standards of the Declaration of Helsinki. All patients and/or their surrogates were informed, and written consent to participate in the trial was obtained before enrolment (MoHP No.: 0018122017. Certificate No.: 1017. Study No.: Ms.24.6.2020).

## Conflicts of interest

The authors declare that they have no conflict of interests, neither financial nor of other sorts.

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