ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
August 2024; 23(4):366-373.
DOI: 10.18502/ijaai.v23i4.16211

Comparative Efficacy of Mometasone Nasal Spray Combined with Different Doses of Desloratadine, and Montelukast in Childhood Allergic Rhinitis: A Randomized Clinical Trial

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Received: 27 February 2024; Received in revised form: 30 April 2024; Accepted: 30 April 2024

ABSTRACT

Allergic rhinitis is a common childhood disease. Although various drugs have been used to treat allergic rhinitis, including nasal corticosteroids, antileukotrienes, and antihistamines, there is still controversy about the optimal dose and the best combination with the highest efficacy. Higher doses of antihistamines are recommended for better control of urticaria, but there is insufficient evidence regarding the efficacy of increased doses of antihistamines in allergic rhinitis. The aim of the study was to evaluate the effectiveness of different drug combinations in the treatment of children with allergic rhinitis.

Sixty-four children with persistent moderate to severe allergic rhinitis were enrolled and randomly divided into 4 groups. All children received mometasone furoate nasal spray once daily. In addition to mometasone, each group received one of the following drugs or drug combinations: daily desloratadine, twice daily desloratadine, montelukast, or a combination of desloratadine and montelukast. The severity of symptoms before and after the intervention was evaluated based on the total nasal symptoms score, including sneezing, nasal congestion, nasal itching, and rhinorrhea.

Sixty patients completed the study. The reduction of nasal congestion score and total nasal symptoms score in the groups receiving desloratadine twice a day and desloratadine plus montelukast was superior to the daily desloratadine group and daily montelukast groups.

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According to this work, the treatment of allergic rhinitis with mometasone nasal spray with desloratadine twice a day or with the combination of desloratadine and montelukast was more effective than other treatment regimens.

Keywords: Allergic rhinitis; Children; Desloratadine; Mometasone furoate; Montelukast

INTRODUCTION

Allergic rhinitis (AR) is a common disease of the upper respiratory tract, the prevalence of which is estimated to be between 5% and 50% and increasing.[1] The pathophysiology of AR is a hypersensitivity reaction that is mainly dependent on immunoglobulin (Ig) E, resulting in the release of mediators such as histamine and leukotrienes and the infiltration of inflammatory cells. These lead to symptoms such as sneezing, rhinorrhea, nasal itching, and congestion.[2] Children are one of the main target groups of this disease due to their narrow nasal passages and immature immune status.[3,4] AR can affect children's long-term quality of life due to sleep disturbance, fatigue, and reduced concentration.[4,5] Avoidance of allergens, along with drug therapy and immunotherapy, are the main approaches to the treatment of AR. Nasal glucocorticoids, antihistamines, and antileukotrienes are the main drugs used to treat this disease. Glucocorticoids can effectively reduce inflammatory responses by stabilizing endothelial cells and lysosomal membranes, reducing the release of inflammatory mediators and antibody synthesis. Intranasal glucocorticoids are one of the treatment priorities in AR due to their strong anti-inflammatory effects.[6,7] Mometasone furoate nasal spray, as a synthetic local glucocorticoid receptor agonist, is one of the most widely used drugs in the treatment of children's AR due to its safety in this population.[8] Antileukotrienes are another group of anti-inflammatory drugs that can inhibit the accumulation of inflammatory cells and reduce vascular permeability and airway smooth muscle contraction.[9] Montelukast sodium is the most applicable antileukotriene that blocks the cysteinyl leukotriene receptor.[10] Antihistamines are one of the most widely used drugs in the treatment of AR and act by preventing the action of histamine on its receptor.[11] The use of antihistamines with a higher dose than usual is recommended to better control chronic urticarial.[12] However, there is still not enough evidence about the effectiveness of increasing the dose of antihistamines in AR. Although the abovementioned drugs are commonly used in the clinical setting, the efficacy, safety, and preference of combination therapy, especially in children with AR, are still controversial. The present research aimed to evaluate the effectiveness of 4 treatment protocols, including intranasal mometasone with a usual dose of desloratadine, a double dose of desloratadine, montelukast, and montelukast plus desloratadine, in childhood AR.

MATERIALS AND METHODS

Study Design

This randomized open-label clinical trial was conducted on children with AR referred to a referral teaching hospital, between March 2022 and March 2023. AR was diagnosed by an allergist based on clinical symptoms (sneezing, rhinorrhea, nasal itching, and nasal abstraction) and physical examination.[1,2] Patients had active disease at the time of referral, and treatment was mandatory.

Inclusion criteria: children aged 6 to 14 years with persistent moderate to severe AR.

Exclusion criteria: lack of consent to enter the study, adenoid hypertrophy, usage of antihistamines, systemic or topical corticosteroids, antileukotrienes, allergen immunotherapy during the last month, and history of allergy to desloratadine, montelukast, and steroids. Additionally, those with a current respiratory infection, acute peptic ulcer, diabetes mellitus, severe heart disease, and all other chronic disorders were excluded.

Demographic and clinical information, including gender, age, medical history, duration of illness, and symptoms, was collected and recorded in the checklists by interviewing children or their parents. Patients were equally assigned to 4 groups using the permuted block method. After that, usinga random sequence generator software, random numbers were obtained, and the order of the blocks in a list was determined. In this way, 16 cases were included in each group (Figure 1). All groups received mometasone nasal spray (Restanex, Sinadarou Laboratories Company, Iran) at a dose of 100 micrograms (one puff in each nostril) daily for 8 weeks.

In addition to mometasone nasal spray, the first group was given desloratadine syroup 2.5 mg/5cc (Neotadine, Dr. Abidi Pharmaceuticals, Iran), and the second group was given desloratadine syroup twice a day (BD). The appropriate dose was prescribed based on the age of the children (2.5 mg for under 12 years and 5 mg for over 12 years). The third group was given montelukast tablets 5 mg [Airokast, Dr. Abidi Pharmaceuticals, Iran], and the fourth group was given desloratadine syroup along with montelukast tablets 5 mg daily. All patients were revisited 2 weeks after the start of the intervention and at the end of 2 months of treatment. The 4 main symptoms of AR (sneezing, nasal congestion, nasal itching, and rhinorrhea) were the variables that were examined to determine the effectiveness of drugs at the beginning and end of the intervention. The severity of the symptoms was evaluated based on the total nasal symptom score (TNSS) method, in which the 4 main symptoms of AR were scored from 0 (absence of the desired symptom) to 3 (severe). In this regard, rhinitis symptoms were measured using a 4-point Likert scale, with zero representing "none" (no significant symptoms), 1 indicating "mild" (symptoms are noticeable but not bothersome), 2 indicating "moderate" (symptoms are noticeable and sometimes annoying but do not interfere with daily activities and sleep), and 3 indicating "severe" (symptoms are usually bothersome and interfere with daily activities and sleep). TNSS was recorded for each patient by the examiner, and the average scores before and after treatment were calculated. The endpoint of the study was the comparison of the improvement rate in the 4 groups.

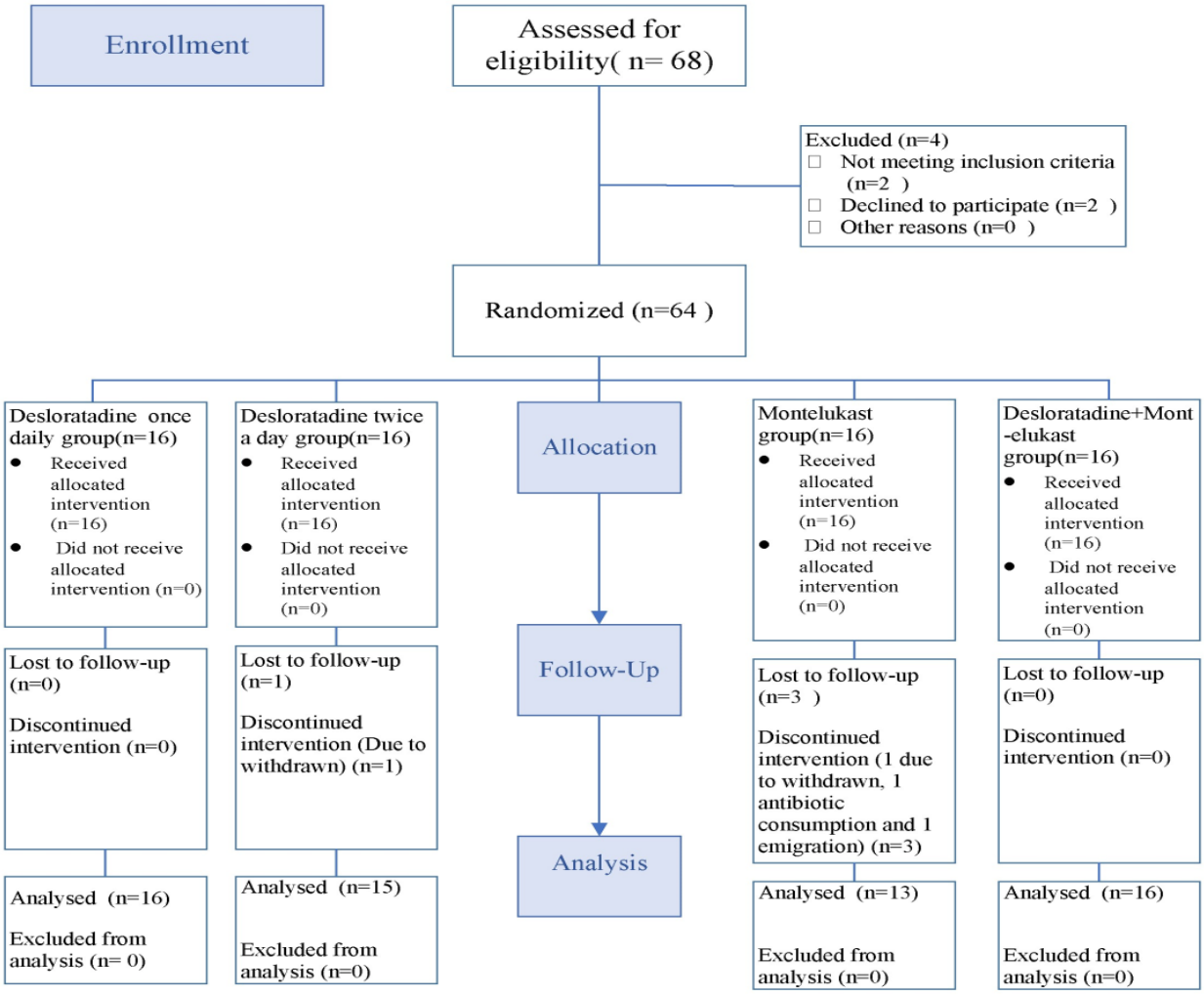

Figure 1. Study design

Ethical Considerations

This survey was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.CHMC.REC.1401.033) and was registered in the Iranian Registry of Clinical Trials (ID: IRCT20211205053277N1). Patients or their parents signed a written informed consent form before enrollment. Patients were allowed to withdraw from the study at any time. Patients' information remained confidential. This study was conducted in accordance with the international principles governing clinical research and the Declaration of Helsinki. Additional costs were not imposed on patients, and the cost of drugs was covered by the researchers.

Statistical Analysis

For statistical analysis, data are presented as mean±standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. The normality of the data was assessed by the Kolmogorov–Smirnov statistical test. Normal data and data that did not appear to have a normal distribution between groups were compared using the analysis of variance (ANOVA) or the Kruskal–Wallis H test, respectively. Whenever the data appeared not to be normally distributed or when the assumption of equal variances was violated across the study groups, the baseline confounding factor effects were adjusted statistically by the analysis of covariance (ANCOVA) test. $p \leq 0.05$ were considered statistically significant. For the statistical analysis, the statistical software SPSS version 28.0 for Windows (IBM, Armonk, New York) was used.

RESULTS

Out of the 68 registered patients, 4 were excluded (1 due to taking prednisolone, 1 due to a common cold in the previous week and the other 2 refused to participate). A total of 64 children were incorporated and divided into 4 groups of 16. Finally, 60 patients completed the study, as follows: in the desloratadine once a day group, 16 patients, desloratadine BD 15 (one patient excluded due to withdrawal), montelukast once on day 13 (one patient due to withdrawal, one due to antibiotic consumption and one who emigrated were excluded) and montelukast plus desloratadine once a day, 16. The study flowchart is shown in Figure 1. Comparison of baseline characteristics between groups showed no differences in sex, mean age, family history of AR, or history of exposure to allergens or pets (Table 1).

In total, 68.3% of the patients had a history of taking different drugs, such as antileukotrienes, antihistamines, and inhaled corticosteroids, and in this regard, there was no statistically significant difference between the groups. However, there was a significant difference in terms of the duration of illness ($p<0.001$) and personal history of allergic disorders ($p=0.03$). The duration of illness was shorter in the daily desloratadine and montelukast groups, and a previous history of allergy in the daily and twice-daily desloratadine groups was more common (Table 1). A comparison of clinical symptoms before and after interventions and their changes is presented in Table 2.

Table 1. Baseline characteristics of the study population

Characteristics	Desloratadine Daily (N=16)	Desloratadine Twice a Day (N=15)	Montelukast (N=13)	Montelukast + Desloratadine (N=16)	*p* [a]
Mean age, years	7.08±4.28	8.36±2.83	6.61±3.64	8.40±2.05	0.36 [b]
Men, n (%)	8 (50.0)	9 (60.0)	3 (23.1)	10 (62.5)	0.15
Disease duration, years	0.80±0.66	2.08±1.82	0.82±0.93	1.85±0.97	0.004 [b]
Exposure to allergens or pets, n (%)	4 (25.0)	6 (40.0)	3 (23.1)	4 (25.0)	0.72
Family history of allergic rhinitis, n (%)	4 (25.0)	2 (13.3)	4 (30.7)	8 (50.0)	0.16
History of allergic disease, n (%)	8 (50.0)	10 (66.7)	2 (15.4)	5 (31.2)	0.035

[a] Chi-square, [b] Analysis of covariance, Quantitative variables are presented as the mean ± standard deviation

Table 2. Changes in clinical symptoms in the different medication groups

Characteristics	Desloratadine Daily (N=16)	Desloratadine Twice a day (N=15)	Montelukast (N=13)	Montelukast+ Desloratadine (N=16)	*p* [b]
Nasal congestion (before)	1.50(0.81)	1.20(1.20)	1.00(0.81)	2.13(1.02)	0.016
Nasal congestion (after)	0.93(0.44)	0.46(0.48)	0.30(0.58)	1.18(0.75)	<0.001
Difference	−0.56 (0.72)	−0.73 (1.01)	−0.70 (0.77)	−0.93 (0.85)	0.014 [c]
p value [a]	0.007	0.01	0.007	0.001	
Rhinorrhea (before)	1.06(0.77)	1.93(0.79)	1.85(0.55)	2.38(0.61)	<0.001
Rhinorrhea (after)	0.64(0.86)	1.01(1.00)	0.60(0.73)	1.12(0.71)	0.23
Difference	−0.42(0.87)	−0.92(0.97)	−1.24(0.80)	−1.25(0.93)	0.89 [c]
p value [a]	0.07	0.03	<0.001	<0.001	
Sneezing (before)	1.56(0.62)	2.47(0.74)	1.38(0.76)	2.25(0.68)	<0.001
Sneezing (after)	1.07(0.67)	0.77(0.93)	0.80(0.68)	1.06(0.68)	0.56
Difference	−0.49(0.50)	−1.68(0.82)	−0.58(0.74)	−1.18(0.54)	0.59 [c]
p value [a]	0.002	<0.001	0.01	<0.001	
Nose itching (before)	1.81(0.98)	1.87(0.83)	1.08(0.86)	1.62(0.88)	.09
Nose itching (after)	1.21(0.53)	0.85(0.74)	1.10(0.86)	1.37(0.71)	0.24
Difference	−0.59(0.98)	−1.01(0.74)	0.02(0.84)	−0.25(0.44)	0.27 [c]
p value [a]	0.02	<0.001	0.92	0.04	
TNSS (before)	5.94(1.84)	7.47(2.80)	5.31(2.17)	8.38(2.09)	0.002
TNSS (after)	3.99(1.63)	3.11(2.91)	2.80(1.90)	4.75(2.26)	0.08
Difference	−1.94(1.40)	−4.35(1.90)	−2.50(1.79)	−3.62(1.50)	0.02 [c]
p value [a]	<0.001	<0.001	<0.001	<0.001	

TNSS, total nasal symptom score. Data are reported as means ± standard errors of the means.
[a] Paired sample *t* test, [b] One-way analysis of variance, [c] Analysis of covariance.

There was no difference in terms of changes in the mean score of rhinorrhea, sneezing, and nasal itching after the intervention. Nasal congestion severity was reduced in the montelukast + desloratadine and twice-daily desloratadine groups more than it was in the daily desloratadine or montelukast groups (p=0.014).

The baseline confounding factor effects of pre-intervention TNSS were adjusted statistically. TNSS reduction was significantly higher in the twice-daily desloratadine and montelukast + desloratadine groups than in the other groups (p=0.02; Figure 2). By comparing different study groups, the reduction in TNSS in the desloratadine BD group was significantly higher than that in the daily desloratadine and daily montelukast groups (p=0.001 and p=0.02, respectively). On the other hand, the reduction in the TNSS in the desloratadine + montelukast group was significantly higher than that in the daily desloratadine group (p=0.03). There was no significant difference between the montelukast plus desloratadine and desloratadine BD groups.

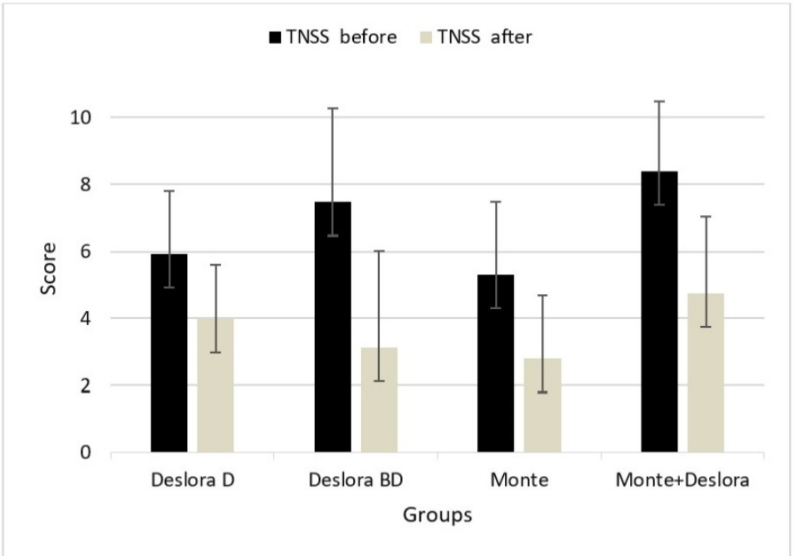

Figure 2. Changes in the total nasal symptom score before and after intervention
TNSS: Total Nasal Symptom Score, Deslora:Desloratadin, Monte: Montelukast, D: Daily, BD: Twice a Day

DISCUSSION

Various protocols have been used to treat AR. The important factor in treatment choice is the long-term effectiveness and fewer side effects. In this regard, a combination of nasal corticosteroids, antileukotrienes, and antihistamines has been evaluated, but their effectiveness and safety are still debatable. In the present analysis, 4 treatment protocols including a combination of the 3 drug categories were evaluated. According to our results, all treatment protocols were effective in improving the symptoms of AR, but combined treatment with montelukast + desloratadine or desloratadine BD was more effective. Dai et al. evaluated the efficacy of mometasone in combination with loratadine or montelukast in childhood AR. Both combinations had a good and similar effect on AR, and no significant difference was observed between the groups. The incidence of adverse drug reactions, including cough, epistaxis, dry mouth, nausea, and vomiting, was significantly lower in the group receiving mometasone+ loratadine.[13]

Jia et al, showed that combination therapy with mometasone furoate along with loratadine or montelukast sodium was effective in childhood AR.[14] In terms of improving nasal congestion, the combination of mometasone with montelukast was more effective, and the combination of mometasone and loratadine was more effective in improving nasal itching and sneezing, while the effect of the 2 combinations was similar for symptoms of runny nose. Overall, both combination regimens were effective in controlling the symptoms and were superior to mometasone alone. In our survey, unlike Jia's study, there was no difference between the groups in the reduction of rhinorrhea, sneezing, and nasal itching, but the groups receiving montelukast + desloratadine and twice-daily desloratadine had a greater reduction in the severity of nasal congestion and TNSS. It seems that adding antihistamines to antileukotrienes or increasing antihistamines dose along with nasal corticosteroids is more effective than other drug combinations in reducing nasal congestion and TNSS.

Anolik et al. evaluated the efficacy of mometasone nasal spray + loratadine versus monotherapy of each agent and placebo in AR. They concluded that adding loratadine to mometasone was no more effective than mometasone alone, and both regimens were more effective than loratadine alone. Additionally, loratadine was more effective than placebo.[15]

Activation of the inflammatory cascade plays an essential role in the exacerbation of AR. In other words, it seems that mucosal irritation caused by exposure to inflammatory factors, followed by inflammatory mucosal damage and increased mucosal permeability, is the basis of the exacerbation of disease symptoms.[16,17] It has been found that the use of combination therapy using nasal corticosteroids, antihistamines, and

antileukotrienes can potentially reduce the levels of inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Following these changes, improvements in ventilation and reductions in airway hyperactivity can be expected.[18] As indicated by Dai et al, combination therapy with mometasone plus loratadine led to lower levels of inflammatory factors, such as IL-6, TNF-α, and IgE, and a greater increase in lung function indexes, including forced expiratory volume in one second (FEV1), FEV1/forced vital capacity (FVC) and peak expiratory flow (PEF), compared with mometasone + montelukast.[13]

Based on the results, it can be concluded that combined treatment with nasal corticosteroids along with twice the usual dose of antihistamine or in combination with antihistamine and antileukotriene can significantly improve the symptoms of AR in children, and this treatment is more effective than combined treatment with nasal corticosteroids along with the usual dose of an antihistamine or antileukotriene.

This work was not blinded, and the results could be affected for this reason. Additionally, due to its single-center nature, it cannot be generalized to the entire population of children. Another limitation was the relatively small sample size. Pulmonary function tests and biological markers involved in the pathogenesis of AR, such as cysteinyl leukotriene levels, were not measured. The measurement of these markers could be helpful in evaluating the impact of different treatment protocols for AR on lung function and biological markers. To better evaluate the role of different treatment protocols in AR, multicenter, blinded trials with larger sample sizes are suggested. It is also suggested to evaluate nonclinical indicators such as biological markers and pulmonary function tests along with clinical evaluations.

STATEMENT OF ETHICS

This study was registered in the Iranian Clinical Trials Registry (ID: IRCT20211205053277N1) and approved by the Research Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.CHMC.REC.1401.033).

FUNDING

There were no funding sources for the study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

We thank all the children and their parents who volunteered their time and information.

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