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Ipratropium Bromide Nasal Spray Relieves Rhinorrhea and Nasal Congestion in Allergic Rhinitis Patients

Vahid Ghobadi Dana[1], Seyed Saeed Hashemi Nazari[2], Ali Pourvali[3], Masoud Habibi[4], Mohsen Fateh[5], Maedeh Arabian[6], Farhad Seif[7], and Ahmad Vosughi Motlagh[8]

[1] Department of Photodynamic, Medical Laser Research Center, Yara Institute, Academic Center for Education, Culture, and Research (ACECR), Tehran, Iran
[2] Department of Epidemiology, Prevention of Cardiovascular Disease Research Center, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Department of Pediatrics, School of Medicine, Arak University of Medical Sciences, Arak, Iran
[4] Department of Photohealing and Regeneration, Medical Laser Research Center, Yara Institute, Academic Center for Education, Culture, and Research (ACECR), Tehran, Iran
[5] Department of Lifestyle Medicine, Medical Laser Research Center, Academic Center for Education, Culture, and Research (ACECR), Tehran, Iran
[6] Cardiogenic Research Center, Rajaei Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
[7] Department of Photodynamic, Medical Laser Research Center, Yara Institute, Academic Center for Education, Culture, and Research (ACECR), Tehran, Iran
[8] Department of Pediatrics, North Khorasan University of Medical Sciences, Bojnurd, Iran

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ABSTRACT

Allergic rhinitis (AR) is a common inflammatory condition characterized by symptoms such as nasal congestion, rhinorrhea, sneezing, and nasal itching, which significantly impact quality of life. Management includes allergen avoidance, pharmacological therapy, and, in severe cases, immunotherapy. Ipratropium bromide, an anticholinergic agent, is primarily used for managing rhinorrhea by inhibiting acetylcholine-mediated secretion in the nasal mucosa.

To evaluate the effects and side effects of ipratropium bromide nasal spray in combination with low-dose budesonide in patients with allergic rhinitis, a double-blind, randomized, placebo-controlled trial was conducted with 126 patients diagnosed with AR. Participants were randomly assigned to receive one of three treatments: Ipranasal 42 µg + budesonide, Ipranasal 21 µg + budesonide, or placebo + budesonide, over a two-week period. Symptom severity was assessed using the ARIA questionnaire and visual analog scale (VAS) for nasal symptoms at baseline and two weeks after the intervention.

Significant reductions in rhinorrhea were observed in the Ipranasal groups compared to the placebo group. Mild side effects, including nasal and oral dryness, were transient and non-significant.

Corresponding Authors: Farhad Seif, PhD;
Department of Photodynamic, Medical Laser Research Center, Academic Center for Education, Culture, and Research (ACECR), P.o.Box: 1315673951Tehran, Iran. Tel/Fax: (+98 21) 6646 2915, Email: Farhad.seif@outlook.com

Ahmad Vosughi Motlagh, MD
Department of Pediatrics, North Khorasan University of Medical Sciences, P.o.Box: 9415867479, Bojnurd, Iran. Tel/Fax: (+98 58) 3222 8111, Email: dr.ahmadvosoughi@yahoo.com

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There were no major differences between the 42 μg and 21 μg groups in terms of efficacy or side effects.

Ipratropium bromide nasal spray effectively reduces rhinorrhea in AR patients, with good tolerability. However, it also had moderate effects on nasal congestion. Combination therapy may enhance symptom control, but further studies are needed to assess long-term efficacy and safety.

Keywords: Allergic rhinitis; Anticholinergic; Budesonide; Ipratropium bromide; Nasal spray; Rhinorrhea

INTRODUCTION

Allergic rhinitis (AR) is a prevalent inflammatory condition affecting a significant portion of the population, characterized by symptoms such as nasal congestion, rhinorrhea (nasal discharge), sneezing, and nasal itching, which can severely impact quality of life.[1] Various allergens, including pollens, dust mites, molds, and certain insects, can trigger AR, leading to heightened risks of comorbid conditions such as asthma.[2] The global prevalence of AR is estimated to range between 10% and 40%.[3] AR is a T helper 2 (T_H2)-dominant disease, in which allergen sensitization occurs in individuals by an immunoglobulin E (IgE)-mediated cascade, leading to mast cell degranulation and the release of inflammatory mediators, including histamine, which are responsible for early-phase symptoms such as sneezing and rhinorrhea. This is followed by a late-phase reaction driven by signature T_H2 cytokines, e.g., interleukin-4 (IL-4), IL-5, and IL-13. Correspondingly, IL-4 induces IgE production, IL-5 is a key cytokine for the recruitment and activation of eosinophils, and IL-13 is responsible for mucosal hypersensitivity and goblet cell hyperplasia, thereby establishing a state of chronic eosinophilic inflammation.[4]

Management of AR includes allergen avoidance, pharmacological therapy, and, in some cases, immunotherapy as a final-line treatment. Among pharmacological options, antihistamines, especially second-generation agents, are widely used as first-line therapy due to their improved safety profile and reduced sedative effects. These drugs block histamine receptors, alleviating key symptoms such as sneezing, pruritus, and rhinorrhea. Intranasal antihistamines provide higher local drug concentrations, enhancing their efficacy in reducing congestion and rhinorrhea. Other therapeutic options include corticosteroids, mast cell stabilizers, leukotriene receptor antagonists, and anticholinergic agents such as ipratropium bromide (IB).[5] Rhinorrhea, or excessive nasal discharge, remains one of the most challenging symptoms to control in AR, primarily driven by cholinergic stimulation of nasal glands. Unlike antihistamines and corticosteroids, which primarily target allergic and inflammatory pathways, IB is a topical anticholinergic agent that directly inhibits acetylcholine-mediated muscarinic receptor activation in the nasal mucosa, reducing excessive nasal secretions.[6]

Studies have demonstrated that IB nasal spray significantly decreases methacholine-induced nasal secretions, supporting its role in managing rhinorrhea associated with AR. While clinical guidelines state that IB does not significantly alleviate nasal congestion or sneezing, some studies suggest potential benefits in reducing these symptoms, albeit to a lesser extent than intranasal corticosteroids.[7] Moreover, its rapid onset of action and localized effects provide an advantage over systemic anticholinergic agents by minimizing adverse effects.[8] Combination therapy, such as IB with beclomethasone, has shown promise in enhancing symptom control without increasing side effects.[9] However, further research is needed to establish standardized long-term treatment protocols and optimize dosing regimens for sustained efficacy and safety.[10] This study aimed to evaluate the specific effects and side effects of IB nasal spray on nasal hypersecretion in patients with AR.

MATERIALS AND METHODS

This study is a double-blind, randomized, placebo-controlled clinical trial designed to evaluate the effect of IB nasal spray (Ipranasal) (Tehran, Iran) in comparison with a placebo in combination with low-dose budesonide nasal spray (Tehran, Iran), in patients with AR (CONSORT flow diagram is shown in Figure 1).

Additionally, the standard ARIA (Allergic Rhinitis and its Impact on Asthma) 2008 questionnaire[11] and a validated Persian questionnaire for AR were completed before the intervention and two weeks after the

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intervention.[12] This questionnaire evaluates five key symptoms: rhinorrhea, sneezing, nasal obstruction, itchy nose, and ocular symptoms. Symptom severity was measured via a visual analog scale (VAS) ranging from 0 to 10 cm, with patients self-reporting scores at two timepoints: prior to treatment (baseline) and following the completion of the intervention period.[13] The Ethics Committee of ACECR approved the protocol (Ethics number: IR.ACECR.IBCRC.REC.1402.005). Furthermore, this study was registered in the Iranian Registry of Clinical Trials (IRCT ID: IRCT20230522058254N1). All patients were aware of the protocol of the study and completed the informed consent form. Written informed consent was obtained from all participants before the study. This study was conducted in accordance with the Helsinki Declaration.

The sample size was calculated based on a previous study by Meltzer et al.[14] With an assumed confidence level (α) of 0.05 and a study power (β) of 90%, the minimum sample size required for each group was determined to be 40 participants. Accounting for the three groups in our study and a potential dropout rate, a total minimum sample size of 140 individuals was estimated. All patients who showed a positive SPT reaction to mix 10 tree, mix 7 grass, mix 5 weed, and mix Dermatophagoides were included in the study. None of the participants took any medication for at least one month prior to the study. Patients had no history of asthma or contact dermatitis. Clinical and immunologic diagnostic criteria used to confirm AR included IgE>100–150 IU, blood eosinophils>5% or 500 cells, and, in severe conditions, nasal eosinophil smear> 5%.[15] Patients were excluded if they were diagnosed with seasonal AR or if AR was not classified as moderate to severe (i.e., it is a mild form of the disease); if they used medication or immunotherapy in the past month; if they were pregnant or aged<18 years or>65 years; if they had AR associated with allergic diseases affecting other organs, such as asthma or skin allergies; or if they had a history of turbinate surgery, nasal septal abnormalities, nasal polyps or tumors, nasal radiotherapy, or recurrent sinusitis.

A questionnaire was used to collect demographic data, clinical characteristics, and allergen profile patterns. Following clinical history-taking and physical examination, the diagnosis of AR was confirmed by a clinical immunology and allergy specialist. Patients were then randomly assigned to one of three groups: Group 1: Ipranasal® 42 µg spray + low-dose budesonide; Group 2: Ipranasal® 21 µg spray + low-dose budesonide; Group 3: Placebo (normal saline) + low-dose budesonide. All groups received two puffs per nostril, three times a day, for two weeks. A skin prick test (SPT) was conducted for allergen screening using a standardized protocol. A positive SPT was defined as a wheal diameter greater than 3 mm compared to the negative control. Eligible patients were randomly allocated to one of three groups using a computer-generated randomization sequence with a fixed block size of six. To ensure allocation concealment, the sequence was prepared by an independent statistician who had no contact with participants or clinical investigators. The assigned treatments (Ipranasal® 42 µg, Ipranasal® 21 µg, or placebo) were packaged in identical, sequentially numbered containers by an independent hospital pharmacist, ensuring that the patients, treating physicians, and outcome assessors were all blinded to the group assignments throughout the study.

Statistical Analysis

All statistical tests were conducted using SPSS software version 22 (IBM, Chicago, USA), and GraphPad Prism 6 (GraphPad, La Jolla, CA) was used for graphical representations. Results were expressed as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was used to assess the normal distribution of data. Categorical variables were reported as frequency and percentage, while continuous variables were presented as mean (SD) or median and interquartile range (IQR) in cases of non-normal distribution. Pearson's chi-square test or Fisher's exact test was used to compare the age distribution between groups. Quantitative data were analyzed using mean and standard deviation (SD). For comparisons between control and AR patient groups, the independent sample t-test was applied. The Kruskal-Wallis test was used to determine the statistical significance of differences among multiple groups. A p value of ≤0.05 was considered statistically significant, corresponding to a 95% confidence interval.

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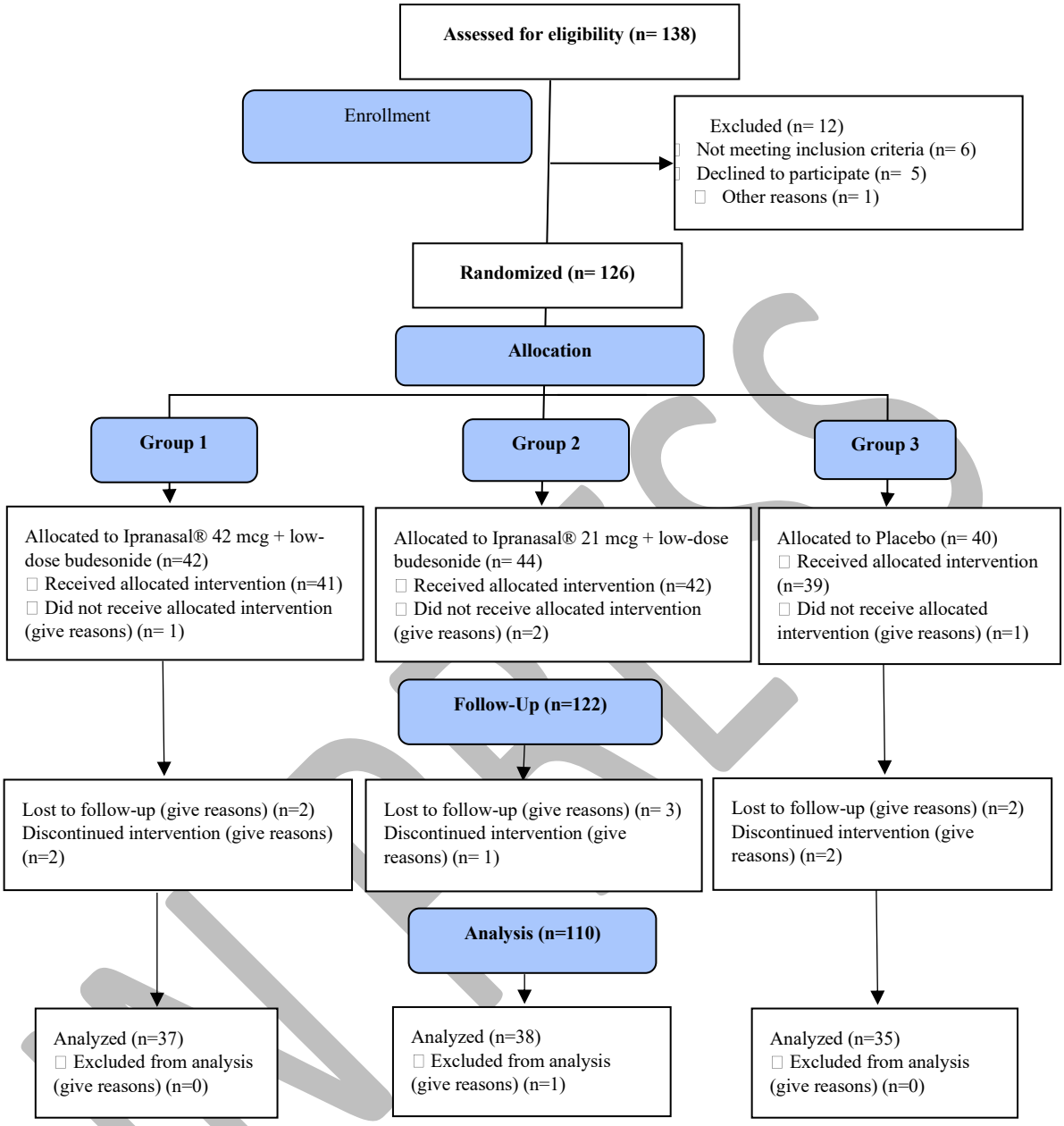

Figure 1. CONSORT 2010 Flow Diagram.

RESULTS

A total of 138 volunteer patients were recruited to the current study. Then, 126 eligible patients who met the inclusion criteria were randomly allocated to the following three groups: Group 1 (Ipranasal 42 µg + low-dose budesonide), Group 2 (Ipranasal 21 µg + low-dose budesonide), and Group 3 (placebo plus low-dose budesonide). Finally, 110 patients completed the trial: 37 (33.7%) patients in Group 1, 38 patients (34.5%) in Group 2, and 35 (31.8%) patients in Group 3. The demographic characteristics of the participants are summarized in Table 1. No significant differences were observed in the groups considering baseline characteristics, including gender and age (p>0.05).

Primary and Secondary Outcomes

At baseline, comparative analysis of the groups in mean AR symptoms, measured by the ARIA questionnaire, indicated that the severity of symptoms in all groups was similar (p>0.05). After treatment, the primary outcome showed that nasal congestion was

significantly reduced in both Ipranasal 42 µg and 21 µg groups compared to the placebo group (p=0.018 and p=0.025, respectively). Likewise, a significant reduction in rhinorrhea was indicated in Ipranasal 42 µg and 21 µg groups in comparison to the placebo group (p=0.002 and p=0.04, respectively). The comparison of sneezing and itching symptoms showed mild improvements in all groups; however, this was not statistically significant (p>0.05). The VAS score for nasal symptoms also demonstrated a significant reduction in symptoms for both the 42 µg and 21 µg Ipranasal groups. However, the 42 µg group showed the greatest reduction in VAS scores for nasal congestion and rhinorrhea (p<0.01). The placebo group showed only a modest improvement that did not reach statistical significance (p>0.05). Results are shown in Table 2.

Mild side effects, such as nasal (5 [4.5%] patients) and oral (2 patients) dryness, were reported in the Ipranasal groups; however, these effects were transient and non-significant. In addition, epistaxis (3 [2.7%] patients) and constipation (1 [0.9%] patients) were also observed (All p>0.05). Figure 2 illustrates the effects on symptoms.

Table 1. Demographic characteristics of the patients

	Ipranasal 42 µg + Budesonide (Group 1)	**Ipranasal 21 µg + Budesonide (Group 2)**	**Normal saline + Budesonide (Group 3)**	***p***
Gender				
Female	20 (54.05%)	19 (51.35%)	19 (54.3%)	>0.05
Male	17 (45.95%)	18 (48.65%)	16 (45.7%)	>0.05
Age	35.47 ± 14.22	31.65 ± 11.87	33.14 ± 12.51	>0.05
Body Weight	64.44 ± 11.58	62.79 ± 12.65	59.18 ± 14.03	>0.05
Height	167.35 ± 8.39	170.45 ± 6.54	169.63±5.29	>0.05
Duration of Rhinorrhea	19.6 ± 8.35	18.89 ± 12.44	21.03 ± 9.62	>0.05
Type of nasal discharge				
Watery	24	21	22	>0.05
Mucoid	13	16	13	>0.05
Family history of allergy				
Positive	31	30	29	>0.05
Negative	6	7	6	>0.05
Smoking	2	2	1	>0.05

NR: not reported.

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Table 2. Comparison of severity of allergic rhinitis symptoms before and after treatment

Symptoms	Group 1 (N=37)	Group 2 (N=38)	Group 3 (N=35)	Group 1 vs Group 2 (*p*)	Group 1 vs Group 3 (*p*)	Group 2 vs Group 3 (*p*)
Rhinorrhea						
Before	6.41 ± 1.84	5.72 ± 2.07	6.89 ± 1.46	>0.05	>0.05	>0.05
After	1.34 ± 0.72	1.47 ± 1.15	5.38 ± 1.29	0.064	0.002	0.005
Congestion						
Before	5.89 ± 2.26	5.37 ± 2.17	6.32 ± 2.05	>0.05	>0.05	>0.05
After	1.63 ± 1.04	1.55 ± 0.93	5.66 ± 2.06	0.26	0.018	0.025
Sneezing						
Before	4.72 ± 0.89	4.63 ± 0.66	4.91 ± 1.23	>0.05	>0.05	>0.05
After	3.44 ± 1.65	3.08 ± 1.74	4.13 ± 1.39	0.47	0.51	0.84
Itching						
Before	4.91 ± 1.35	4.81 ± 0.88	4.54 ± 0.75	>0.05	>0.05	>0.05
After	2.83 ± 2.09	3.24 ± 1.89	3.85 ± 0.65	0.09	0.26	0.41
Side effects						
Nose Dryness	3	2	4	>0.05	>0.05	>0.05
Mouth Dryness	1	1	0	>0.05	>0.05	>0.05
Epistaxis	2	1	1	>0.05	>0.05	>0.05
Constipation	1	0	0	>0.05	>0.05	>0.05

[a]Group 1: Ipranasal 42 µg spray + low-dose budesonide; Group 2: Ipranasal® 21 µg spray + low-dose budesonide; Group 3: Placebo (normal saline) + low-dose budesonide; N: number.

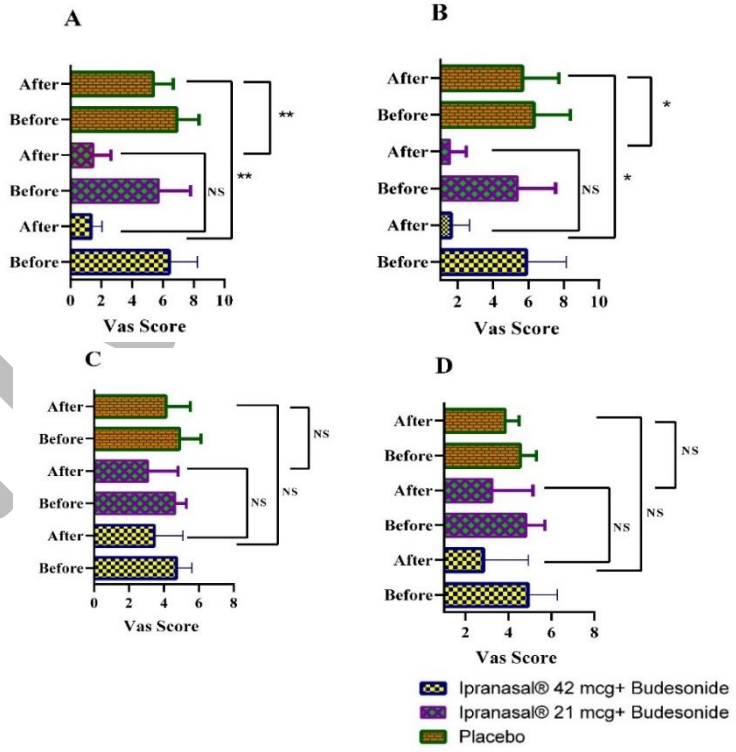

Figure 2. Effect of Ipranasal 42 µg and Ipranasal® 21 µg versus placebo on rhinorrhea (A), congestion (B), sneezing (C), and itching (D).

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DISCUSSION

The main findings of the current study indicate that IB nasal spray significantly reduces rhinorrhea associated with perennial rhinitis. The results also showed that IB significantly alleviates sneezing and subjective rhinorrhea severity compared with placebo or no treatment, with a strong therapeutic effect observed across a range of dosage strengths (42 to 84 µg per nostril).[16,17] Furthermore, the treatment was generally well tolerated, with only a few adverse effects like nasal dryness and blood-tinged mucus, though these were infrequent and not considered serious.[17,18]

The effectiveness of IB in managing rhinorrhea is consistent with its mechanism of action as an anticholinergic agent, which blocks the secretion of mucus in the nasal passages by inhibiting acetylcholine, a neurotransmitter responsible for glandular secretion. However, it did not show significant improvement in nasal congestion, a finding that aligns with previous studies.[19] IB serves as a competitive antagonist at muscarinic receptors in the airways. Its fundamental bronchodilating effect is mediated by blocking the M3 receptors located on smooth muscle cells of the airways, which prominently trigger acetylcholine-induced bronchoconstriction. By inhibiting the M3 receptor, IB prevents the intracellular signaling cascade, resulting in reduced smooth muscle contraction. IB is a short-acting agent, characterized by a faster dissociation rate from the M3 receptor complex (half-life of approximately 0.3 hours). It is a non-selective antagonist with high affinity for both M1 and M3 receptors. Interestingly, its quaternary ammonium structure limits systemic absorption, thereby restricting the antimuscarinic impacts on the airways and reducing systemic side effects. The combination of IB with nasal steroids, such as beclomethasone, has also been found to further reduce rhinorrhea, supporting the notion that IB's efficacy can be enhanced when used in combination with other therapies targeting inflammation and other symptoms of rhinitis.[7]

The present study's findings align with previous research examining the effect of IB in various rhinitis conditions, including perennial allergic rhinitis. For instance, a study by Dockhorn et al recently reported that the combination of IB with beclomethasone provided faster relief from rhinorrhea and superior overall effectiveness compared to each treatment used alone. This supports the idea that IB has a rapid onset of action, which was similarly observed in our study.[20] Additionally, the advantages of IB in reducing rhinorrhea without a significant impact on nasal congestion have been found in several other studies. Although some studies report that IB can prevent hypersensitivity reactions rather than improve congestion,[21] we found a significant reduction in nasal congestion. It may be due to a combination of IB and low-dose budesonide, not IB per se. Moreover, the trial by Meltzer et al focusing on perennial AR demonstrated a similar reduction in the severity and duration of rhinorrhea with IB nasal spray, especially at the higher dose of 42 µg per nostril. This shows that IB's efficacy in treating rhinorrhea is consistent across different populations and is not significantly affected by underlying allergic or nonallergic rhinitis. The finding that IB did not significantly improve symptoms of nasal congestion further supports the assertion that its primary role lies in addressing rhinorrhea rather than broader symptoms of nasal obstruction.[14] In contrast, other studies examining the effects of IB in studies of airway hyperresponsiveness and methacholine challenges revealed minimal improvements in airway response, further confirming that while IB is effective for managing rhinorrhea, its effects on nasal congestion and other aspects of nasal and airway reactivity may be limited.[22] This suggests that IB's mechanism of action is primarily confined to the reduction of mucus secretion rather than influencing broader inflammatory or bronchial responses.

Despite the overall similarities in findings, some studies have reported slightly different results, particularly in terms of the impact on nasal congestion. For example, the study by Reid et al showed that IB had a modest effect on increasing the provocative concentration of methacholine, indicating a subtle influence on airway responsiveness.[23] This is different from our results, where IB did not show a marked reduction in nasal congestion, likely because congestion is primarily driven by inflammatory processes (such as those targeted by steroids) rather than by excessive secretion of mucus alone. Mild side effects, such as nasal and oral dryness, epistaxis, and constipation, were observed in the Ipranasal® groups; nevertheless, these effects were transient and non-significant. Consistent with our findings, previous studies showed that IB caused effective rhinorrhea reduction in patients with

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allergic and nonallergic rhinitis with minimal side effects.[24,25]

Moreover, variations in study design and participant populations, such as the inclusion of individuals with more severe cases of rhinitis, may also contribute to slight differences in the effectiveness observed across studies. For instance, the study by Hayden et al emphasized that IB significantly reduced nasal discharge in healthy individuals with mild to moderate cold symptoms, but patients with more severe congestion or longer durations of symptoms may respond differently.[16] Lastly, the discrepancy in adverse effects, such as nasal dryness and blood-tinged mucus, which were more common in our study compared to other trials, may be due to dosage variations or differences in participant sensitivity. It is worth noting that these adverse effects were generally mild and well-tolerated, aligning with previous safety data for IB use in the nasal form.[20] This study has some limitations. The short study duration (14 days) does not provide insight into long-term effects or safety. A longer trial duration would be valuable in several respects. Firstly, it would allow for a more robust evaluation of the true efficacy of nasal budesonide, whose maximal anti-inflammatory effects on the nasal mucosa may take several weeks to fully manifest. Secondly, an extended study could reveal whether the initial benefits of the IB doses are maintained or if tolerance develops. Furthermore, a longer observation period is essential to detect less common adverse events and better understand the long-term safety of this specific combination therapy. We strongly suggest that future studies with extended follow-up periods are necessary to confirm these preliminary findings and establish definitive guidelines for chronic AR management.

Ipratropium bromide (IB) nasal spray is an effective and well-tolerated therapy, especially for rhinorrhea in patients suffering from allergic rhinitis (AR). Its main advantage is an obvious reduction in nasal discharge, making it a valuable adjunctive therapy to intranasal corticosteroids, which target the underlying inflammation and other symptoms like congestion. In clinical practice, our findings demonstrate the use of IB as a targeted add-on treatment for patients whose rhinorrhea is not adequately controlled with corticosteroid monotherapy. Future research should focus on long-term safety and efficacy studies to solidify the role of IB in AR management. Furthermore, investigations into optimal dosing strategies and IB applications in various AR phenotypes will be helpful for personalizing treatment and maximizing therapeutic outcomes.

STATEMENT OF ETHICS

The Ethics Committee of ACECR approved the protocol (Ethics number: IR.ACECR.IBCRC.REC.1402.005). Furthermore, this study was registered in the Iranian Registry of Clinical Trials (IRCT ID: IRCT20230522058254N1). All patients were aware of the protocol of the study and completed the informed consent form. Written informed consent was obtained from all participants before the study. This study was conducted in accordance with the Helsinki Declaration.

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CONFLICT OF INTEREST

The authors declare that placebo, Ipranasal, and budesonide were provided by Ideh Darou Teb Pharmaceutical Company. The company had no role in the study design, data collection, analysis, interpretation, or manuscript writing.

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Not applicable.

DATA AVAILABILITY

The data are available on a reasonable request from the corresponding author.

AI ASSISTANCE DISCLOSURE

The authors use ChatGPT to edit the language of this manuscript.

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