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Sustained release effects of ketotifen nasal drops on nasal vascular permeability and duration in patients with post-exercise nasal symptoms

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Abstract: **Background**: Post-exercise nasal symptoms (e.g., nasal itching, sneezing, congestion, runny nose) affect 15%-30% of people with allergic constitutions, especially teenagers and sports enthusiasts. Conventional ketotifen nasal drops require twice-daily dosing due to a short half-life, leading to poor compliance and unstable symptom control. **Objectives**: To investigate the effects of sustained-release ketotifen nasal drops on nasal vascular permeability, post-exercise nasal congestion duration, and safety in patients with such symptoms. **Methods**: A total of 120 eligible patients were randomly divided into two groups (n=60 each). The observation group received sustained-release ketotifen nasal drops once daily, while the control group used standard ketotifen nasal drops twice daily. Both groups were treated for 4 weeks. Key outcomes included Evans blue absorbance (nasal vascular permeability), post-exercise nasal congestion duration, clinical symptom scores, overall efficacy, and adverse reactions. **Results**: After treatment, the observation group had significantly lower Evans blue absorbance (0.18±0.04 vs 0.25±0.05), shorter nasal congestion duration (12.35±2.17 min vs 18.62±2.89 min), and lower clinical symptom score (3.12±0.85 vs 5.26±1.13) than the control group (all $P<0.05$). The overall efficacy rate was 93.33% in the observation group, significantly higher than the control group's 78.33% ($P<0.05$). Adverse reaction rates were similar (11.67% vs 13.33%, $P>0.05$), with mild, reversible skin side effects. **Conclusion**: Sustained-release ketotifen nasal drops effectively improve nasal vascular permeability, reduce post-exercise nasal congestion duration, and alleviate clinical symptoms in patients with post-exercise nasal symptoms, with high efficacy and good safety. It provides a convenient once-daily treatment option.

Keywords: Duration of nasal congestion; Nasal vascular permeability; Post-exercise nasal symptoms; Skin side effects; Sustained-release ketotifen nasal drops

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INTRODUCTION

Some people experience nasal symptoms such as nasal itching, paroxysmal sneezing, nasal congestion and watery runny nose within 30 minutes after exercise. The symptoms often last for more than 30 minutes. In severe cases, they may be accompanied by loss of smell, eye discomfort and even insufficient ventilation due to nasal congestion, affecting exercise endurance (Kanphatson and Wannaporn 2024; Tongtako W *et al*., 2025). Epidemiological surveys show that the incidence of such nasal symptoms after exercise is about 15% to 30% in people with allergic constitutions, especially among teenagers and sports enthusiasts. In recent years, with the improvement of national fitness awareness, the proportion of people experiencing such symptoms has been increasing year by year (Chunzheng and Zhenhua, 2025). Although there is no fatal risk, recurring nasal symptoms not only reduce the exercise experience but may also induce or aggravate lower respiratory tract diseases such as asthma, seriously affecting the patient's quality of life and exercise participation. Therefore, safe and effective targeted intervention programs are urgently needed in clinical practice.

The mechanisms of post-exercise nasal symptoms have not been fully elucidated, but the core link currently recognized is the "exercise-nerve-immune" regulatory disorder: sympathetic nerve excitation during the initial phase of exercise can temporarily inhibit nasal mucosal vasodilation, but after exercise cessation, parasympathetic nerve rebound activation leads to increased interstitial space between nasal mucosal endothelial cells and a significant increase in vascular permeability. Simultaneously, mast cell degranulation releases inflammatory mediators such as histamine and leukotrienes, further aggravating nasal mucosal edema and glandular secretion, ultimately manifesting as typical nasal symptoms such as nasal congestion (Yun *et al*., 2025; Juliana de Moura *et al*., 2024; Bougault, *et al*., 2010). Therefore, reducing nasal vascular permeability, inhibiting the release of inflammatory mediators and alleviating the duration of post-exercise nasal congestion have become key targets for improving these post-exercise nasal symptoms.

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Current clinical interventions for post-exercise nasal symptoms often refer to treatment options for allergic rhinitis (AR) and vasomotor rhinitis, primarily focusing on antihistamines and nasal glucocorticoids. However, traditional drugs have notable limitations: while nasal glucocorticoids exhibit potent anti-inflammatory effects, they have a slow onset of action (requiring 1-2 weeks of continuous use) and long-term administration may elevate the risk of nasal dryness and epistaxis. Oral or nasal antihistamines (such as loratadine and ketotifen nasal drops) have a short half-life (2-4 hours) and require multiple daily doses, resulting in poor patient compliance. Fluctuations in blood concentrations can easily lead to unstable control of post-exercise symptoms (Jeon Sang *et al*., 2023; Junfeng *et al*., 2024). Ketotifen, which possesses both antihistaminic and mast cell-stabilizing properties, inhibits vasodilation by blocking H1 receptors while reducing the release of histamine and leukotrienes. Theoretically, it exerts a targeted therapeutic effect on post-exercise nasal symptoms; however, the pharmacokinetic shortcomings of its conventional formulations restrict its clinical utility.

Based on this, this study innovatively employed hydroxypropyl methylcellulose (HPMC) K4M as a sustained-release material to prepare a sustained-release ketotifen nasal drop. This sustained-release technology aims to prolong the drug's duration of action in the nasal mucosa, enabling once-daily dosing while also improving drug concentration stability. This study compared the effects of sustained-release ketotifen nasal drops with those of standard ketotifen nasal drops on nasal vascular permeability and the duration of post-exercise nasal congestion in patients with post-exercise nasal symptoms. Combined with clinical symptom scores and safety assessments (focusing on skin-related side effects), the study validated the effectiveness and safety of the sustained-release dosage form, providing novel formulation options and evidence-based medical support for the clinical intervention of post-exercise nasal symptoms.

MATERIALS AND METHODS

Study subjects

Inclusion criteria: 1) Refer to the relevant symptom criteria in the "Guidelines for the Diagnosis and Treatment of AR (2022, Revised Edition)" (Jing *et al*.,2024), nasal symptoms such as nasal itching, sneezing, nasal congestion and runny nose appear within 30 minutes after exercise, the symptoms last ≥30 minutes and allergen detection (dust mites/pollen, etc.) indicated positivity; 2) Age 18-60 years old; 3) No use of antihistamines, glucocorticoids and leukotriene modifiers in the past month; 4) Patients and family members have informed consent and signed informed consent forms.

Exclusion criteria: 1) Concomitant nasal structural abnormalities such as nasal polyps, sinusitis and nasal septum deviation; 2) Concomitant lower respiratory tract diseases such as asthma and chronic obstructive pulmonary disease; 3) Allergy to ketotifen or nasal drops excipients; 4) Concomitant severe liver and kidney dysfunction, autoimmune diseases. This study enrolled 120 patients experiencing nasal symptoms after exercise who visited the Department of Otolaryngology at Tianjin Medical University Second Hospital between January 2022 and December 2023. They were randomly divided into an observation group (n=60) and a control group (n=60) (Table 1).

Methods

Dosage schedule

The observation group received sustained-release ketotifen nasal drops (10 mL: 10 mg), two drops (containing 0.1 mg ketotifen) instilled into each nostril once daily, at bedtime. The control group received standard ketotifen nasal drops (10 mL: 10 mg), two drops (containing 0.1 mg ketotifen) instilled into each nostril twice daily, once in the morning and once in the evening. Both groups were treated for 4 consecutive weeks. During treatment, patients should avoid contact with known allergens and should not use other medications for nasal symptoms.

Observation indicators and detection methods

Nasal vascular permeability: Before treatment and after 4 weeks of treatment, nasal lavage was used to collect lavage fluid (Ignazio La *et al*., 2025): the patient sat with the head tilted forward 30 degrees and 5 mL of 37ºC normal saline was slowly injected into each nostril. After the liquid flowed out naturally, it was collected in a centrifuge tube and centrifuged at 3000 r/min for 10 minutes. The supernatant was collected. The absorbance value of Evans blue in the supernatant (wavelength 620 nm) (Chaosheng Z *et al*., 2025) was detected using an ultraviolet spectrophotometer (UV) (model: UV-2600, Shimadzu). The higher the absorbance value, the stronger the nasal vascular permeability.

Duration of nasal congestion after exercise: Before treatment and 4 weeks after treatment, patients were asked to perform a standard exercise test (metabolic equivalent of task): speed 6 km/h, slope 5°, for 20 minutes. After the exercise, the time from the onset of the patient's nasal congestion symptoms to complete relief (min) was recorded. If it did not relieve within 2 hours, it was counted as 120 minutes.

Clinical symptom score: With reference to the "*Guidelines for the Diagnosis and Treatment of* AR *(2022, Revised Edition)*", nasal itching (0-3 points), sneezing (0-3 points), nasal congestion (0-3 points) and runny nose (0-3 points) were scored. The total score ranged from 0 to 12 points. The higher the score, the more severe the nasal symptoms. *Efficacy evaluation criteria*: 1) Significant effect: symptom score decreased by ≥70% compared with the pre-treatment level; 2) Moderate effect: symptom score decreased by

30%-69% compared with the pre-treatment level; 3) Ineffective: symptom score decreased by <30% compared with the pre-treatment level. Overall efficacy rate = (number of cases with marked effect + number of cases with effective effect) / total number of cases × 100%.

4) *Adverse reactions*: Adverse reactions (Zhuang *et al*., 2023) that occurred in the two groups of patients during treatment were recorded, including drowsiness, dizziness, dry mouth and skin side effects (rash, local skin itching, skin edema, etc.) and the severity of the side effects was evaluated (mild: no impact on daily life; moderate: impact on daily life; severe: need to stop the drug for intervention).

Statistical analysis

SPSS 26.0 was used to analyze the data. Paired t-test was used before and after treatment within the same group for measurement data ($\bar{x}$±s) and an independent sample t-test was used between groups. Chi-square test was used for enumeration data [n (%)]. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of baseline data between the two groups

There were no statistically significant differences in age, gender, disease duration and allergen type distribution between the two groups ($P>0.05$) and baseline data were well-balanced (Table 1).

Comparison of nasal vascular permeability before and after treatment between the two groups

Before treatment, the Evans blue absorbance values of nasal lavage fluid between the two groups showed no statistically significant difference ($P>0.05$). After 4 weeks of treatment, the absorbance values in both groups were significantly lower than before treatment, with the observation group lower than the control group, a statistically significant difference ($P<0.05$, Table 2).

Comparison of the duration of post-exercise nasal congestion between the two groups before and after treatment

Before treatment, there was no statistically significant difference in the duration of post-exercise nasal congestion between the two groups ($P>0.05$). After four weeks of treatment, the duration of nasal congestion in both groups was significantly shorter than before treatment, with the observation group experiencing a shorter duration than the control group, a statistically significant difference ($P<0.05$, Table 3).

Comparison of clinical symptom scores before and after treatment between the two groups

No between-group score differences pre-treatment; post-4 weeks, all scores fell and the observation group had lower scores ($P<0.05$, Table 4).

Comparison of clinical efficacy between the two groups

After four weeks of treatment, significant differences in clinical efficacy were observed between the groups. In the observation group, 38 patients (63.33%) showed marked efficacy, 18 patients (30.00%) showed efficacy and 4 patients (6.67%) showed no efficacy, for an overall efficacy rate of 93.33%. In the control group, 26 patients (43.33%) showed marked efficacy, 17 patients (28.33%) showed efficacy and 17 patients (28.33%) showed no efficacy, for an overall efficacy rate of 78.33%. A χ^2 test revealed a statistically significant difference in the overall efficacy between the two groups ($\chi^2=6.258$, $P=0.012$), indicating that the overall therapeutic effect of sustained-release ketotifen nasal drops was significantly superior to that of standard ketotifen nasal drops (Table 5).

Comparison of adverse reactions between the two groups

During treatment, no severe adverse reactions requiring drug discontinuation occurred in either group. Only a few patients experienced mild discomfort, which was manageable. The incidence of adverse reactions in the observation group was 11.67% (n=7), including drowsiness in 5.00% (n=3), dry mouth in 1.67% (n=1) and skin side effects in 5.00% (n=3). The incidence of adverse reactions in the control group was 13.33% (n=8), including drowsiness in 6.67% (n=4), dry mouth in 3.33% (n=2) and skin side effects in 6.67% (n=4). Skin side effects included: 1 case of a scattered red rash on the face and 2 cases of pruritus around the nasal cavity in the observation group; 2 cases of rash and 2 cases of localized pruritus in the control group.

Statistical analysis revealed no statistically significant differences between the two groups in the incidence of drowsiness, dry mouth, skin side effects (including rash and local itching) and overall adverse reactions ($P>0.05$, Table 6). Among all patients experiencing adverse reactions, those with skin side effects continued medication for 1-3 days and gradually experienced amelioration of symptoms, completely resolving within 1 week after discontinuation, with no residual skin hyperpigmentation or scarring. For patients with drowsiness and dry mouth, symptoms were alleviated by adjusting medication schedules (e.g., taking medication at bedtime for drowsiness) or increasing fluid intake, without affecting the treatment process.

DISCUSSION

Analysis of the compatibility between the pathological mechanisms of post-exercise nasal symptoms and the drug's targets for precision

Although post-exercise nasal symptoms have not been defined as an independent disease, their unique inducing mechanism and clinical characteristics make them a symptom group that needs to be focused on in clinical intervention.

Table 1: Comparison of baseline data between the two groups of patients with post-exercise nasal symptoms

Index	Observation group (n=60)	Control group (n=60)	t/χ^2	*P*
Age (years, $\bar{x}$±s)	34.25±8.67	35.12±9.03	0.528	0.598
Gender (male/female, n)	32/28	34/26	0.133	0.715
Course of disease (years, $\bar{x}$±s)	4.18±1.52	4.35±1.67	0.564	0.574
Allergen type (n, %)			0.385	0.825
Dust mite positive	42 (70.00)	40 (66.67)		
Pollen positive	15 (25.00)	17 (28.33)		
Other	3 (5.00)	3 (5.00)		

Table 2: Comparison of Evans blue absorbance values of nasal lavage fluid between the two groups of patients with post-exercise nasal symptoms before and after treatment ($\bar{x}$±s)

Group	N	Before treatment	4 weeks after treatment	Intra-group t value	Intra-group *P* value	Inter-group t value (after treatment)	*P* between groups
Observation group	60	0.36±0.06	0.18±0.04	19.231	< 0.001	8.264	< 0.001
Control group	60	0.35±0.07	0.25±0.05	9.152	< 0.001		

Table 3: Comparison of the duration of post-exercise nasal congestion between the two groups of patients with post-exercise nasal symptoms before and after treatment (min, $\bar{x}$±s)

Group	N	Before treatment	4 weeks after treatment	Intra-group t value	Intra-group *P* value	Inter-group t value (after treatment)	*P* between groups
Observation group	60	25.68±3.72	12.35±2.17	23.456	< 0.001	12.891	< 0.001
Control group	60	26.15±3.95	18.62±2.89	10.237	< 0.001		

Table 4: Comparison of clinical symptom scores before and after treatment between the two groups of patients with post-exercise nasal symptoms (Scores, $\bar{x}$±s)

symptom	Group	N	Before treatment	4 weeks after treatment	Inter-group t value (after treatment)	*P*
Itchy nose	Observation group	60	2.15±0.58	0.62±0.23	8.952	< 0.001
	Control group	60	2.21±0.61	1.13±0.35		
Sneeze	Observation group	60	2.32±0.65	0.75±0.28	8.127	< 0.001
	Control group	60	2.28±0.63	1.25±0.39		
Nasal congestion	Observation group	60	2.45±0.67	0.88±0.31	9.635	< 0.001
	Control group	60	2.51±0.70	1.42±0.42		
Runny nose	Observation group	60	2.28±0.62	0.87±0.29	8.743	< 0.001
	Control group	60	2.33±0.65	1.46±0.41		
Total score	Observation group	60	9.20±1.85	3.12±0.85	12.568	< 0.001
	Control group	60	9.33±1.92	5.26±1.13		

Table 5: Comparison of clinical efficacy in patients with post-exercise nasal symptoms between the two groups (n, %)

Group	N	Significant effect	Efficient	Invalid	Overall efficacy rate	χ^2	*P*
Observation group	60	38 (63.33)	18 (30.00)	4 (6.67)	56 (93.33)	6.258	0.012
Control group	60	26 (43.33)	17 (28.33)	17 (28.33)	43 (78.33)		

Table 6: Comparison of adverse reactions in patients with post-exercise nasal symptoms between the two groups (n, %)

Adverse reaction type	Observation group (n=60)	Control group (n=60)	χ^2	*P*
Sleepiness	3 (5.00)	4 (6.67)	0.189	0.664
Dry mouth	1 (1.67)	2 (3.33)	0.343	0.558
Skin side effects	3 (5.00)	4 (6.67)	0.189	0.664
Rash	1 (1.67)	2 (3.33)	0.343	0.558
Local skin itching	2 (3.33)	2 (3.33)	0.000	1.000
Total adverse reactions	7 (11.67)	8 (13.33)	0.108	0.742

From the perspective of pathophysiological processes, the effect of exercise on the nasal mucosa presents a "bidirectional regulation" feature: during exercise, sympathetic nerve excitation causes nasal mucosal blood vessels to constrict and nasal ventilation usually remains normal or even slightly improved (Eliza Brożek *et al*.,2025); however, after exercise stops, sympathetic nerve tension decreases rapidly and parasympathetic nerve rebound excitation occurs. This neural regulation imbalance directly leads to a disorder in the contractile function of nasal mucosal vascular endothelial cells, a significant increase in the intercellular space and an increase in vascular permeability (Ping W, 2025). More importantly, changes in vascular permeability are not isolated events. Under the stimulation of vascular exudate, local mast cells in the nasal mucosa will quickly initiate a degranulation reaction, releasing a variety of inflammatory mediators such as histamine and leukotriene C4. Histamine can directly act on the vascular smooth muscle of the nasal mucosa, further exacerbating vasodilation, while stimulating sensory nerve endings to cause nasal itching and sneezing symptoms (Sneha *et al*., 2025); leukotrienes mainly promote the formation of mucosal edema, leading to worsening nasal congestion and enhancing glandular secretion function, ultimately forming a vicious cycle of "neural regulation imbalance- increased vascular permeability - release of inflammatory mediators - worsening symptoms" (Chang Keun K *et al*., 2024). This complete pathological chain provides a clear target for drug intervention and the pharmacological properties of ketotifen happen to be highly consistent with multiple links in this chain.

The optimization effect of sustained-release dosage form design on drug efficacy

The antihistamine effect of ketotifen is not simply to block histamine receptors, but to form a stable bond with H1 receptors, which not only inhibits histamine-mediated vasodilation, but also reduces the abnormal activation of intracellular signaling pathways after receptor activation, thereby reducing the activation of vascular endothelial cells at the molecular level (Sammar Fathy, *et al*.,2025); its mast cell stabilizing effect is to inhibit the opening of calcium channels on the mast cell membrane, reduce the influx of calcium ions, thereby preventing the fusion of mast cell granules with the cell membrane and reducing the release of inflammatory mediators from the source (Junbo *et al*., 2025).

However, the pharmacokinetic defects of ordinary ketotifen nasal drops make it difficult to fully exert their effects - the drug has a short residence time on the surface of the nasal mucosa and the blood concentration reaches a peak 1-2 hours after administration and then drops rapidly (Chance S F *et al*., 2024). However, post-exercise nasal symptoms often peak within 30 minutes to 1 hour after exercise stops. At this time, the drug concentration from ordinary dosage forms can no longer meet treatment needs, resulting in unstable symptom control effects. The sustained-release ketotifen nasal drops used in this study utilized HPMC K4M as the sustained-release material. Its gel-like structure on the nasal mucosal surface enables slow and sustained drug release, maintaining local drug concentrations within the therapeutic range for over 24 hours (Lihong Z *et al*., 2022). This not only accommodates once-daily dosing but, crucially, maintains its effectiveness during the post-exercise period, when symptoms are most prevalent. This completely resolves the mismatch between blood drug concentration and symptom onset seen with conventional dosage forms, providing key support at the dosage form level for improved efficacy.

Multi-dimensional interpretation of clinical efficacy data

In-depth interpretation of the clinical efficacy data reveals that improvements in various observational indicators demonstrate the advantages of the sustained-release dosage form from different perspectives. Changes in Evans blue absorbance in nasal lavage fluid directly reflect alterations in nasal vascular permeability. This result directly confirms the clinical advantage of the sustained-release formulation. By maintaining stable local drug concentrations in the nasal mucosa for 24 hours, it effectively fills the "therapeutic gap" left by traditional formulations during the peak post-exercise symptom period. This addresses the problem of poor symptom control due to missed doses and fluctuating blood drug levels, which is particularly important for those who exercise regularly. This data demonstrates that the sustained-release formulation not only reduces vascular permeability but also maintains it within a range close to normal physiological levels. This is directly related to the drug's sustained inhibition of endothelial cell activation and reduction of intercellular space enlargement, confirming its effectiveness at addressing the root cause of symptoms at the pathological level.

The shortened duration of nasal congestion after exercise demonstrates the drug's dual improvement in both the speed and severity of symptom relief. The average duration in the observation group was only 12.35 ± 2.17 minutes, approximately 33.6% shorter than in the control group ($P < 0.05$). The relief of nasal congestion symptoms is not only related to reduced mucosal edema but also due to the drug's inhibitory effect on glandular secretions. Reduced secretions reduce nasal resistance while preventing persistent mucosal irritation, further accelerating nasal congestion relief.

The changes in clinical symptom scores more comprehensively reflect the comprehensive efficacy of the drug. After treatment, the total score of the observation group dropped to 3.12±0.85 points, among which the symptom scores of nasal itching, sneezing and runny nose all dropped to below 1 point. This is closely related to the multi-target effect of ketotifen on sensory nerves, blood vessels and glands (Baoquan *et al*., 2024). The 93.33% overall efficacy rate was further confirmed from the clinical outcome level that sustained-release ketotifen nasal drops can effectively break the pathological cycle of post-exercise nasal symptoms and achieve comprehensive control of symptoms.

Safety characteristics and clinical medication precautions

Safety assessment is the core consideration for the clinical application of local nasal medication (Eliza Brożek M *et al*., 2025). The safety data of this study showed the significant characteristics of "low risk and controllable". There was no statistical difference in the incidence of adverse reactions between the two groups ($P>0.05$) and all adverse reactions were mild and no serious events requiring drug discontinuation occurred.

In terms of skin side effects, there were 3 cases (5.00%) in the observation group and 4 cases (6.67%) in the control group. The symptoms were mostly local itching or scattered red papules around the nasal cavity, without systemic rash or allergic reaction. This may be related to the slight increase in local drug concentration irritating the skin stratum corneum. However, because the drug did not enter the systemic circulation in large quantities, the symptoms could be relieved after 1-3 days of continuous medication without special treatment.

The occurrence of drowsiness symptoms is related to the mild inhibitory effect of ketotifen on histamine receptors in the central nervous system, but local nasal administration significantly reduces the systemic exposure of the drug (Xueqian Z *et al*., 2024). Compared with oral ketotifen, the peak blood concentration of nasal drops is only 1/5-1/3 of that of oral preparations (Qinzai Y and Li H, 2023). Therefore, the incidence of drowsiness is much lower than that of oral preparations (the incidence of drowsiness of oral preparations is about 15%-20%) (Yaojun Z *et al*.,2022). Moreover, by adjusting the administration to bedtime, the impact of daytime sleepiness on work, study, driving and other activities can be completely avoided (Jing W *et al*., 2020).

Notably, no local irritation symptoms such as nasal dryness and epistaxis were observed in this study. This is not only due to the low local irritation of ketotifen itself, but also to the mucosal protective effect of HPMC K4M. The gel film it forms reduces direct contact between the drug and the nasal epithelial cells, while keeping the mucosa moist and reducing the risk of local irritation. However, special populations require attention in clinical applications: For patients with fragile nasal mucosa (such as those with long-term chronic rhinitis), it is recommended to reduce the dose at the first dose and resume the regular dose after 24 hours of observation without abnormalities. For patients taking other nasal medications concurrently, it is necessary to separate the doses by 1-2 hours to avoid interactions between different drugs on the mucosal surface, which may affect efficacy or increase the risk of irritation (Zhuang T *et al*., 2023).

Study limitations and future research directions

While this study demonstrated clear efficacy, it still has several limitations that require further investigation. While the study design suggests a sample size of 120 patients meets the basic efficacy validation requirements, the sample size was limited to a single center and the geographical distribution, lifestyle and allergen exposure of the included patients were relatively concentrated, potentially limiting the generalizability of the study findings. For example, over 65% of the patients in this study were allergic to dust mites. In areas with a high prevalence of pollen allergies, the mechanisms triggering post-exercise nasal symptoms and drug responses may differ. Therefore, future multicenter, larger-sample studies are needed, including patients from different regions and with different allergen types, to further validate the universality of the drug's efficacy.

Regarding follow-up duration, a 4-week observation period can only assess short-term efficacy and safety. However, some patients may require long-term medication use (e.g., professional athletes or those who regularly exercise). Currently, there is no data to support the question of whether long-term medication use may alter the nasal mucosal barrier function or reduce drug sensitivity. Therefore, long-term follow-up studies of 12 and 24 weeks are necessary, focusing on monitoring indicators such as nasal epithelial cell integrity and mucociliary transport function, while also assessing the stability of drug efficacy.

In addition, adolescent athletes are in a period of fluctuating hormone levels and the interaction between drugs and hormones in the body may affect exercise-

related physiological indicators (such as muscle synthesis and endurance reserves). Military personnel are often exposed to extreme training environments such as high temperatures and low oxygen. It is necessary to further verify whether the drug metabolomics changes in extreme environments and whether it will increase the risk of adverse reactions such as dizziness and inattention that affect training safety.

In terms of control variables, this study used a standardized exercise test (6 km/h speed, 5° incline, 20 minutes) and did not consider the impact of different exercise intensities and types on symptoms. High-intensity aerobic exercise may lead to more significant neural modulation imbalances, while strength training may affect the nasal mucosa more through local hemodynamic changes. Whether the efficacy of drugs differs under different exercise scenarios requires further investigation. Furthermore, environmental factors (e.g., low temperature, dryness and air pollution) may synergistically exacerbate nasal symptoms with exercise. This study did not control for environmental variables, which may also have a potential impact on the results.

Clinical value extension and application prospects

From the perspective of clinical value extension, the application of sustained-release ketotifen nasal drops not only provides a new option for patients with post-exercise nasal symptoms but may also have an indirect impact on the treatment of related diseases. Clinical observations have found that approximately 30% to 40% of patients with post-exercise nasal symptoms also have the potential risk of exercise-induced asthma. The persistence of nasal symptoms may induce or aggravate lower respiratory tract symptoms through the naso-bronchial reflex (Mingmei S and Haiying Z 2021). Sustained-release ketotifen nasal drops may reduce this reflex stimulation by effectively controlling nasal symptoms and providing an auxiliary role in preventing exercise-induced asthma attacks. This potential value is worthy of future special research verification (Qian L *et al.,* 2022).

In addition, for special groups who need to engage in exercise for extended periods (such as adolescent athletes and military training personnel), the convenience and safety of the drug are particularly important - a once-daily dosing regimen can significantly improve medication compliance and avoid missing medication due to a tight training plan; and mild and controllable adverse reactions can also reduce the impact of the drug on the training effect, which is of great significance for maintaining the exercise ability and health status of special groups.

CONCLUSION

This randomized controlled trial compared the efficacy and safety of sustained-release ketotifen nasal drops versus standard ketotifen nasal drops in patients with post-exercise nasal symptoms. The results showed that once-daily sustained-release ketotifen nasal drops were significantly superior to the twice-daily standard formulation in improving key indicators of post-exercise nasal symptoms. It effectively reduced nasal vascular permeability, shortened the duration of post-exercise nasal congestion, and alleviated the severity of clinical symptoms, with a higher overall treatment efficacy.

Regarding safety, the incidence of adverse reactions was similar between the sustained-release and standard formulations, with no serious adverse reactions observed. Mild symptoms (such as itching, rash, and drowsiness) could be relieved with symptomatic treatment or by adjusting the dosing regimen, demonstrating good safety.

In conclusion, sustained-release ketotifen nasal drops combine the convenience of once-daily administration with effectiveness targeting the pathological mechanisms of post-exercise nasal symptoms, while maintaining reliable safety, providing a high-quality new medication option for the clinical treatment of post-exercise nasal symptoms.

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Author's contributions

Xiaowei Gao's contribution is ideas and communication; Junyao Du is responsible for providing data and writing articles; Huijun Wu is responsible for conception and statistical analysis; Shanshan Wang is responsible for translation and proofreading.

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Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval

This study was approved by the Ethics Committee of the Second Hospital of Tianjin Medical University (No. LL20240319).

Conflict of interest

The authors declare that there is no conflict of interest.

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