# Comparing the effects of ketotifen fumarate eye drops and ketotifen oral pills on symptom severity and quality of life in patients with allergic rhinitis: a double-blind randomized clinical trial

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***Background:*** **Allergic rhinitis is a chronic inflammatory disease of nasal mucosa. Previous studies have shown the therapeutic effects of ketotifen eye drops on allergic conjunctivitis and rhinitis patients. This study was designed to compare the effects of ketotifen drops and oral ketotifen pills on symptoms and quality of life in allergic rhinitis patients.**

***Methods:*** **In this double-blind randomized clinical trial, patients with mild allergic rhinitis who were referred to the allergy clinic of Baqiyatallah Hospital from March to April 2014 were randomly allocated to 2 groups; the first group received ketotifen drops (1 drop every 12 hours) with placebo pills (2 pills daily), and the second group received placebo eye drops with ketotifen pills for 4 weeks. Symptoms (sneezing, runny nose, itching, and nasal obstruction) severity were examined and Rhinitis Quality of Life Questionnaire (RQLQ) scores were evaluated in the second and fourth weeks.**

***Results:*** **A total of 140 patients were evaluated in 2 groups. The mean age was 30.33 years. There were no significant differences in demographic data between the groups ($p > 0.05$). Both groups showed a significant improvement in rhinorrhea, nasal congestion, nasal itching, coughing, sneezing, RQLQ, and nasal smear eosinophil percent compared to baseline amounts ($p < 0.05$). Improvements were significantly more in the drops group ($p < 0.05$).**

***Conclusion:*** **Because of the absence of systemic complications in ketotifen eye drops in patients with allergic rhinitis and their easy availability in Iran, using this medication instead of systemic therapies is suggested. Nevertheless, more studies are required to evaluate the long-term effects of using this drug and the recurrence rate of symptoms.** © 2015 ARS-AAOA, LLC.

*Key Words:*
**allergic rhinitis; ketotifen fumarate eye drops; ketotifen pills; quality of life; symptoms**

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Allergic rhinitis is an inflammatory disease of nasal mucosa related to the function of immunoglobulin E (IgE), involving 10% to 20% of Americans.[1] Symptoms, such as rhinorrhea, sneezing, and nasal congestion could be periodic, seasonal, or permanent.[2,3] Patients usually complain about eye and ear symptoms, cough, increase in daily sleep and lethargy, inconveniences in job and educational activities[4] due to sleep disorders, and microarousals due to nasal obstruction by allergens that evidently affect daily activities.[5,6] These sequels of allergic rhinitis have different effects on patients' quality of life.[7]

Common medicines used in the treatment of allergic rhinitis include antihistamines, corticosteroids, leukotriene receptor antagonists, decongestants, anticholinergics, and cromolyn sodium.[8] Applying these medications depends on the disease severity, type of allergic rhinitis, episodic or permanent, physician's preference, and finally following approved guidelines.[9]

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Ketotifen is an $H_1$ blocker antihistamine that prevents releasing histamine and inflammatory mediators from mast cells and eosinophil. Ketotifen also prevents infiltration, activation, and degranulation of eosinophils. It is used in different conditions such as asthma, allergic rhinitis, and conjunctivitis. Ketotifen lets the air flow more freely in airways by decreasing inflammation.[10]

Ketotifen is used in the treatment of allergic conjunctivitis and itchy eyes. Its therapeutic dosage is 1 drop every 8 to 12 hours.[11–13] Crampton[13] showed that ketotifen eye drops decrease nasal symptoms of patients with rhinoconjunctivitis. Haicl and Cerná[14] reported that ketotifen fumarate is effective in the treatment of seasonal allergic conjunctivitis as monotherapy.

Van Cauwenberge et al.[15] reported that ketotifn tablets (Zaditen) decreased nose itching, rhinorrhea, and sneezing but did not have a significant effect on diminishing nasal obstruction. Spangler et al.[16] showed that eye exposure to allergens causes secondary nasal symptoms as an indicator of movement of allergens, inflammatory mediators, and ophtalmic therapeutic drugs toward nasal space.

Noticing the therapeutic effects of ketotifen and recommendations for its use, the present study compared the effects of ketotifen pills and drops (intranasal) on decreasing allergic rhinitis symptoms, such as sneezing and rhinorrhea, after 2 and 4 weeks of treatment. Nasal ketotifen drops and spray are expensive therapies and not fully reachable in Iran, but recently ketotifen eye drops have been manufactured in Iran and are not expensive.

Nasal spray supplies a larger surface area absorption and less drug loss to the pharynx compared to drops.[17] Apart from cost and availability, there are no more advantages for ketotifen eye drops over its nasal formulation. Because systemic absorption of drugs is poor through the eyes,[18,19] domestically manufactured ketotifen eye drops were used intranasally. Nasal drug administration has some advantage including direct absorption to the systemic blood supply, increasing bioavailability of drug, fast onset of action, no need for sterility, and no known contraindication for using eye drops intranasally.[20,21] The rate of quality of life improvement was also compared between the 2 treatment methods.

## Patients and methods

This randomized clinical trial was registered at Baqiyatallah University of Medical Sciences Ethics Committee (meeting No.31, July 2013) and Iranian Registry of Clinical Trial (reference code: IRCT2014051617413N3). Figure 1 shows a flowchart of the trial. A total of 150 patients with mild allergic rhinitis were needed for this evaluation. Patients who were referred to the Allergy Clinic of Baqiyatallah University of Medical Sciences from March to April 2014 were enrolled in the study without any age and gender limitations. A written informed consent was obtained from all patients. Allergic rhinitis was approved by clinical examination, history, and immediate hypersensitivity skin testing (skin-prick test).[22] Patients without sleep disturbance, disruptions in school or work, impairment of daily activities, leisure and/or sport activities, and troublesome symptoms were considered as patients with mild allergic rhinitis. Patients consuming antihistamines and corticosteroids, refractory to antihistamines and leukotriene receptor antagonists, patients with asthma, acute and chronic rhinosinusitis, polyposis, consuming tricyclic antidepressants, allergy to ketotifen, and patients not willing to participate in the experiment were excluded from the study. The patients were randomized to 2 groups: the first group used ketotifen fumarate 0.025% drops (1 drop in each side of nose every 12 hours) with placebo pills (every 12 hours), and the second group used placebo drops (1 drop every 12 hours) with ketotifen pills (1 mg every 12 hours with food). The block randomization was accomplished using the clinic's automatic turn system and patients were randomized into 2 groups by their clinic turns at a ratio of 1:1 and a block size of 4. The patients were evaluated for endoscopic presentations, symptoms (sneezing, runny nose, itching, and nasal obstruction) severity score (visual analogue scale [VAS] score = 0 to 10), quality of life, and eosinophil percent for nasal smears, within the 4 weeks of treatment in 3 visits. Collected data were compared between the 2 groups.

The VAS was used to check symptom severity. The Persian version of 0 to 6 scored Rhinitis Quality of Life Questionnaire (RQLQ) was used to evaluate the quality of life at the beginning of the treatment and after treatment.[23] Moreover, the 0 to 12 scored Lund-Kennedy endoscopic score was used in endoscopic evaluations before and after treatment.[24] During nasal endoscopy, a smear was taken from the posterior part of middle turbinate and was spread out on a glass. The smear was stained using the Giemsa method and the percentage of eosinophils was determined by an experienced cytologist.

### Statistical analysis

Data was analyzed using SPSS software version 21 (SPSS Inc., Chicago, IL) for Microsoft Windows. Normal distributed variables (approved by 1-sample Kolmogorov-Smirnov test) were compared using independent sample *t* test between the groups and paired sample *t* test within the groups. Mann-Whitney *U* test was used between the groups and Wilcoxon test was run within the groups in variables without normal distribution. The chi square test was used to compare categorical variables in the 2 groups.

Paired sample *t* test and its nonparametric equivalent were used to compare the values before and after treatment within the groups.

## Results

A total of 140 patients (63 males and 67 females) with a mean age of 30.33 ± 9.81 years and mean body mass index

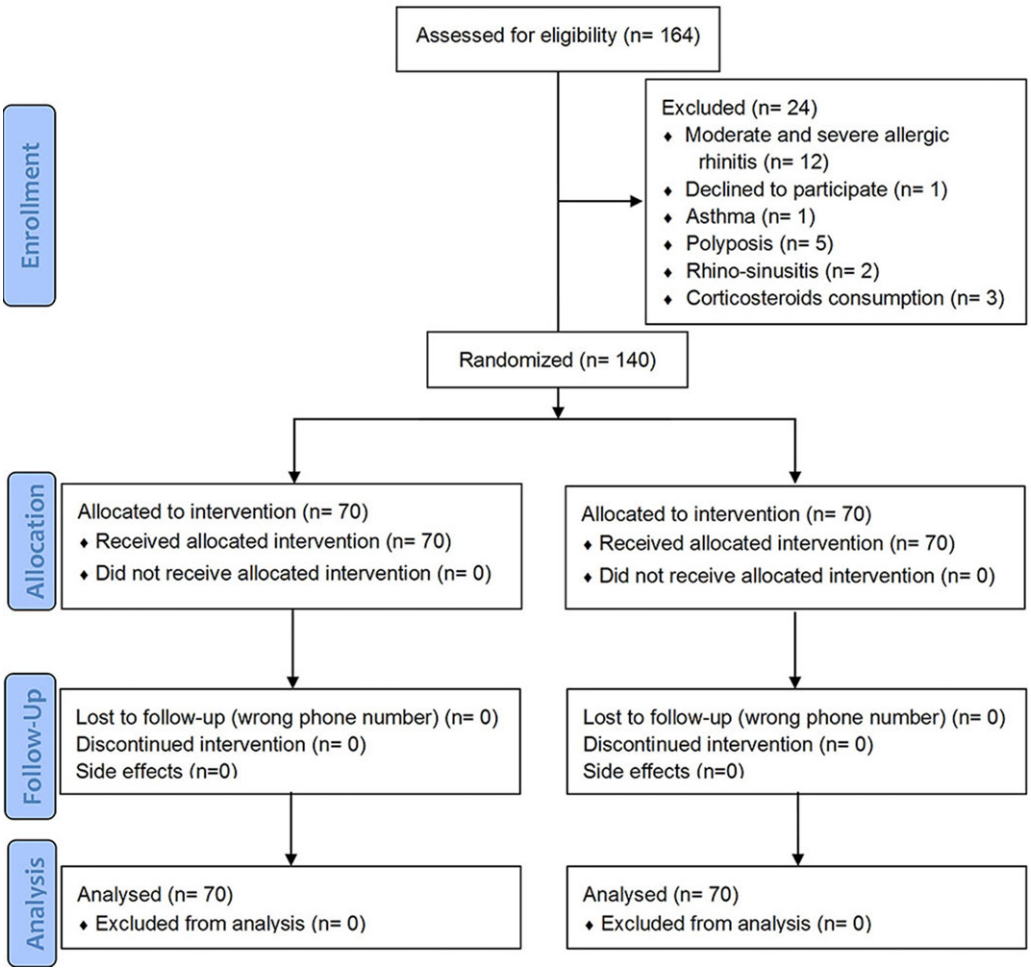


**FIGURE 1.** Study flowchart.

(BMI) of 23.14 ± 2.62 kg/m$^2$ were evaluated. There were no significant differences in demographic data between the groups ($p > 0.05$). The chief complaint was runny nose in 38.6% of the drops group and 22.9% of the pill group; the complaint was nasal obstruction in 25.7% of the drops group and 57.1% of the pill group. Both complaints were observed in 35.7% of the drops group and 20% of the pill group ($p = 0.01$). Type of allergy was intermittent in 81.4% of the drops group and 68.6% of the pill group. Seasonal allergy was found in 15.7% of the drops group and 31.4% of the pill group and constant allergic rhinitis was 2.9% in the drops group ($p = 0.04$). Twenty-four percent of the patients had a history of allergy and allergic rhinitis in their family. Patients' characteristics are shown in Table 1.

## Symptoms

Runny nose severity score decreased 2.65 ± 0.96 units in the drops group and 1.71 ± 0.57 units in the pill group in comparison to the baseline amount. Changes in runny nose severity score were significantly more in the drops group in comparison to the pill group ($p < 0.001$). Nasal obstruction severity decreased 2 ± 0.93 units in the drops group

**TABLE 1.** Patient characteristics

| Variable | Ketotifen drop (n = 70) | Ketotifen pill (n = 70) | *p* |
|---|---|---|---|
| Age, years, mean (SD) | 31.74 (9.19) | 28.9 (10.26) | 0.09 |
| Male, n (%) | 32 (44.3) | 31 (45.7) | 0.5 |
| BMI, kg/m$^2$, mean (SD) | 22.98 (3.07) | 23.29 (2.09) | 0.48 |
| Chief complaint, n (%) | | | 0.01 |
| Runny nose | 27 (38.6) | 16 (22.9) | |
| Nasal obstruction | 18 (25.7) | 40 (57.1) | |
| Both | 25 (35.7) | 14 (20) | |
| Kind of allergic rhinitis, n (%) | | | 0.04 |
| Intermittent | 57 (81.4) | 48 (68.6) | |
| Seasonal | 11 (15.7) | 22 (31.4) | |
| Constant | 2 (2.9) | 0 (0) | |
| Family history, n (%) | 15 (21.4) | 19 (27.1) | 0.56 |

BMI = body mass index; SD = standard deviation.

and 1.45 ± 0.65 units in the pill group in comparison to the baseline amount. Change in nasal obstruction severity was significantly higher in the drops group ($p < 0.001$). Before the treatment, 66 patients in the drops group and 52 patients in the pill group had itchy nose ($p = 0.02$). At the end of the study, itchy nose was observed in 2 patients in the drops group and 10 patients in the pill group ($p = 0.01$).

Decrease in itchy nose rate was significantly higher in the drops group ($p < 0.001$). Prior to the treatment, 61 patients in the drops group and 49 patients in the pill group had itchy pharynx ($p = 0.03$). At the end of the study, itchy pharynx was observed in 1 patient in the drops group and 16 patients in the pill group ($p < 0.001$). Decrease in itchy pharynx rate was significantly higher in the drops group ($p < 0.001$). Prior to the treatment, 62 patients in the drops group and 45 patients in the pill group had sneezing ($p = 0.01$). At the end of the study, sneezing was reported in 12 patients in the drops group and 8 patients in the pill group ($p = 0.23$). Changes in sneezing, red eye, and cough rates were not significantly different between the 2 groups ($p > 0.05$). Changes in patients' symptoms are presented in Table 2.

### Clinical and laboratory findings

The mean Lund-Kennedy endoscopic score decreased 3.17 ± 0.91 units in the drops group and 2.51 ± 0.94 units in the pill group. In comparison to the baseline amount, this change was significantly higher in the drops group ($p < 0.001$). The mean nasal smear eosinophil percent decreased 5.3 ± 2.7 units in the drops group and 2.9 ± 5.9 units in the pill group. Compared to the baseline amount, this reduction was significantly greater in the drops group ($p = 0.002$). Changes in Lund-Kennedy endoscopic score and nasal smear eosinophil percent during the 4 weeks are shown in Table 3.

### Quality of life

Quality of life was significantly lower in the drops group at the beginning of the study ($p = 0.014$). At the end of the study, quality of life did not differ between the groups ($p = 784$). The mean changes of quality of life score decreased 1.25 ± 0.48 units in the drops group and 0.98 ± 0.53 units in the pill group. In comparison to the baseline amount, these reductions were significantly higher in the drops group ($p = 0.002$). Changes in quality of life during the 4 weeks are shown in Table 3.

Age, gender, and BMI did not show significant correlations with quality of life in general and within the groups ($p > 0.05$). No side effects, headache, sedation, nausea, and fatigue, were reported during or after the follow-up period.

## Discussion

In the present study, despite proper randomization, the drops group had more severe allergic rhinitis before

**TABLE 2.** Patient symptoms

| Symptoms | Ketotifen drop (n = 70) | Ketotifen pill (n = 70) | *p* |
|---|---|---|---|
| Runny nose severity (0–10), mean (SD) | | | |
| Before | 3.88 (0.67) | 2.51 (0.73) | 0.01 |
| Second week | 1.54 (1.36) | 1.05 (0.67) | 0.009 |
| Fourth week | 1.22 (1.4) | 0.8 (0.57) | 0.025 |
| Changes | −2.65 (0.96) | −1.71 (0.57) | <0.001 |
| Nasal obstruction severity (0–10), mean (SD) | | | |
| Before | 3.1 (0.93) | 2.17 (0.88) | 0.02 |
| Second week | 1.18 (1.08) | 1.03 (0.76) | 0.28 |
| Fourth week | 1.0 (1.1) | 0.7 (0.7) | 0.08 |
| Changes | −2.0 (0.93) | −1.45 (0.65) | <0.001 |
| Itchy nose, n (%) | | | |
| Before | 66 (94.3) | 52 (74.3) | 0.02 |
| Second week | 13 (18.6) | 42 (60) | 0.001 |
| Fourth week | 2 (2.9) | 10 (14.3) | 0.01 |
| Changes | −64 (−91.4) | −42 (−60) | <0.001 |
| Itchy throat, n (%) | | | |
| Before | 61 (87.1) | 49 (70) | 0.03 |
| Second week | 13 (18.6) | 32 (45.7) | 0.001 |
| Fourth week | 1 (1.4) | 16 (22.8) | <0.001 |
| Changes | −60 (−85.7) | −33 (−74.1) | <0.001 |
| Sneezing, n (%) | | | |
| Before | 62 (88.6) | 45 (63.2) | 0.01 |
| Second week | 25 (35.7) | 32 (45.7) | 0.15 |
| Fourth week | 12 (17.1) | 8 (11.4) | 0.23 |
| Changes | −50 (−71.4) | −37 (−52.9) | 0.368 |
| Red eyes, n (%) | | | |
| Before | 29 (41.4) | 17 (24.3) | 0.02 |
| Second week | 5 (7.1) | 5 (7.1) | – |
| Fourth week | 2 (2.9) | 1 (1.4) | 0.5 |
| Changes | −27 (−38.6) | −16 (−22.9) | 0.101 |
| Cough, n (%) | | | |
| Before | 14 (20) | 17 (24.3) | 0.61 |
| Second week | 6 (8.6) | 11 (15.7) | 0.35 |
| Fourth week | 0 (0) | 0 (0) | – |
| Changes | −14 (−20) | −17 (−24.3) | 0.61 |

SD = standard deviation.

**TABLE 3.** Comparison of clinical and laboratory findings and quality of life between the groups*

| | Ketotifen drop (n = 70) | Ketotifen pill (n = 70) | *p* |
|---|---|---|---|
| Endoscopic score (0–12) | | | |
| Before | 4.77 (1.68) | 5.08 (1.52) | 0.25 |
| After | 1.6 (1.34) | 2.57 (1.26) | <0.001 |
| Changes | −3.17 (0.91) | −2.51 (0.94) | <0.001 |
| Nasal smear eosinophil percent | | | |
| Before | 7.23 (3.2) | 8.57 (4.5) | 0.047 |
| After | 1.97 (0.9) | 5.7 (5.2) | <0.001 |
| Changes | −5.3 (2.7) | −2.9 (5.9) | 0.002 |
| Quality of life (0–6) | | | |
| Before | 2.91 (0.668) | 2.62 (0.693) | 0.014 |
| After | 1.66 (0.242) | 1.65 (0.269) | 0.784 |
| Changes | −1.25 (0.479) | −0.98 (0.529) | 0.002 |

*Values are mean (SD) percent change.
SD = standard deviation.

intervention in terms of symptoms severity, nasal smear, eosinophil count, and quality of life. Both groups had a significant decrease in rhinorrhea and nasal obstruction severity at the end of the study, but the drops group showed a significantly greater decrease. The same result was observed for nose and throat itch. The 2 groups showed a significantly lower rate of sneezing and eye redness compared to the basal rate. Cough, red eyes, and sneezing were not significantly different between the 2 groups, but they decreased in both groups after the treatment. The obtained results indicated the faster effects of drops compared to pills. The score of nose endoscopy significantly decreased in both groups with a significantly higher decrease in the drops group. The quality of life of patients in the drops group was clearly higher before the intervention, but at the end of the study both groups showed a significant decrease in this respect (30 and 23 points for the drops and pill groups, respectively). Smear of nasal secretions showed 5.3% and 2.9% decreases in eosinophils in the drops and pill groups, respectively.

In the existing literature, there are no exactly similar studies comparing ketotifen pill and drops on controlling allergic rhinitis symptoms.

Lai et al.[25] compared the effect of oral ketotifen, oxatomide, and cetirizine on quality of life, severity of symptoms, and percentage of eosinophils in nasal smear in childhood perennial allergic rhinitis. They used a 4-point scale (0 to 3) for evaluation of symptoms (rhinorrhea, congestion, nasal itching, and red eye) and the RQLQ quality of life questionnaire. All therapeutic groups showed significant improvement in nasal and ocular symptoms compared with placebo. Cetirizine showed a better effect on rhinorrhea, nasal obstruction, and nasal smear eosinophil proportion.

Crampton[26] compared the effect of ketotifen ophthalmic solution and placebo on controlling acute-phase symptoms of allergic rhinoconjunctivitis induced by the conjunctival allergen challenge model. Crampton[26] evaluated standardized scales of sneezing (0 to 2), postnasal drip, rhinorrhea, nasal congestion (0 to 3), and nose and throat itch (0 to 1) and showed the significant effect of ketotifen on prevention of nasal signs and symptoms in comparison to the placebo.

Horak et al.[27] showed that ketotifen eye drops adjunctive to mometasone furoate nasal spray provides greater relief from both ocular and nasal signs and symptoms than mometasone furoate nasal spray alone.

Greiner and Minno[28] showed the superiority of ketotifen ophthalmic solutions in prevention of ocular itching using the conjunctival allergen challenge (CAC) model compared to nedocromil sodium. In another study, ketotifen eye drops were better than placebo drops in treating nasal allergic symptoms after ocular conjunctival allergen challenge model.[29]

Crampton's study[13] showed the effect of ketotifen eye drops and desloratadine pills on controlling ocular tearing, eyelid swelling, and nasal signs and symptoms, and additional benefits in prescribing both drugs at the same time.

Avunduk et al.[30] evaluated inflammatory markers more than clinical manifestations. They showed that ketotifen and olopatadine ophthalmic solutions have the same effects on decreasing inflammatory markers, itching, and tearing. Torkildsen et al.[31] also noted the effectiveness of ketotifen fumarate eye drops in preventing ocular itching after conjunctival allergen challenge.

Borazan et al.[32] examined the efficacy of olopatadine, ketotifen, epinastine, and emedastine ophthalmic solutions in controlling symptoms of seasonal allergic conjunctivitis but did not report a significant difference between them.

In another study, ketotifen fumarate and olopatadine eye drops had similar therapeutic effects on controlling eye burning and tearing of allergic conjunctivitis in the second week, but in the fourth week olopatadine presented better therapeutic effects.[33]

Figus et al.[34] showed the same results for the therapeutic effects of ketotifen drops compared with cromolyn, diclofenac, epinastine, fluorometholone, levocabastine, naphazoline, and olopatadine in patients with allergic conjunctivitis. They showed that epinastine, fluorometholone, ketotifen, and olopatadine are more effective in decreasing patients' symptoms.

Sarker et al.[35] observed significant effects for both ketotifen and olopatadine hydrochloride drops but indicated the superiority of olopatadine in short-term management of allergic conjunctivitis.

Mortemousque et al.[36] reported no significant differences in the therapeutic effects of ketotifen and olopatadine ophthalmic solutions in seasonal allergic conjunctivitis. They

also showed that ketotifen drops have better ocular tolerance compared to olopatadine.

Because of the absence of systemic complications in ketotifen eye drops in patients with allergic rhinitis and their easy availability in Iran, using this medication instead of systemic therapies is suggested. However, more studies are required to evaluate long-term effects of using this drug and the recurrence rate of symptoms. Further studies are recommended with larger sample sizes and longer follow-up periods. It is also suggested that the serum level of IgE and peripheral blood eosinophil percentage be assessed in addition to eye redness and other ophthalmic symptoms. Ketotifen eye drops have fewer side effects compared to other common systemic drugs for allergic rhinitis; therefore, using these domestically manufactured drops instead of systemic therapeutic medications and other expensive drops is recommended. Furthermore, further studies are suggested to compare ketotifen nasal spray with other allergic rhinitis therapies.

## Conclusion

This study showed significant decreases in rhinorrhea, nasal obstruction, nasal itching, coughing, sneezing, quality of life, and nasal smear eosinophil percent compared to baseline amounts in both groups. Reductions in rhinorrhea, nasal obstruction, nasal and pharyngeal itching, quality of life, and nasal smear eosinophil percent were significantly more in the ketotifen drops group in comparison to the ketotifen pill group.

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