

Effect of Nasal Steroid Treatment on Dry Eye in Geriatric Population with Rhinitis: Case Control Study

Riniti Olan Geriatrik Popülasyonda Nazal Steroid Tedavisinin Kuru Göz Üzerine Etkisi: Vaka Kontrol Çalışması

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ABSTRACT Objective: To evaluate the effect of nasal steroid treatment on dry eye and rhinitis in the geriatric population presenting with both rhinitis and dry eye. **Material and Methods:** In this single-center clinical study, 31 (62 eyes) older adults (age >65 years) with rhinitis and dry eye were included. The symptoms and findings of the patients were compared with the Total Nasal Symptom Score (TNSS), the Ocular Surface Disease Index (OSDI), Schirmer I test, and the tear break-up time (TBUT) before and after nasal steroid treatment (beclomethasone dipropionate), with a dose of 2×2 puff (50 µg) for 4 weeks. Intraocular pressure (IOP) values were also measured before and after treatment. All rhinitis cases (allergic and non-allergic) in the geriatric population were included in the study. **Results:** TNSS, OSDI score, and Schirmer and TBUT values improved significantly after nasal steroid treatment (beclomethasone dipropionate) ($p<0.001$). No significant change was detected in IOP values in the right or left eyes ($p=0.608$ and $p=0.062$, respectively). **Conclusion:** Nasal steroid treatment at the recommended doses can be effective for both rhinitis and dry eye symptoms without affecting the IOP in older adults, thus may reduce the need for multiple medications for dry eye symptoms. Our study should be supported with further studies designed in larger series.

Keywords: Dry eye; nasal steroid; older adults; rhinitis; Schirmer test

ÖZET Amaç: Bu çalışmanın amacı, riniti ve kuru gözü olan geriatrik popülasyonda nazal steroid tedavisinin kuru göz ve rinit üzerindeki etkisini değerlendirmektir. **Gereç ve Yöntemler:** Bu tek merkezli klinik çalışmaya riniti ve kuru gözü olan 31 (62 göz) yaşlı erişkin (yaş >65) dâhil edildi. Hastaların semptom ve bulguları; 4 hafta boyunca 2×2 puf (50 µg) dozunda nazal steroid (beklometazon dipropiyonat) kullanılarak, tedaviden önce ve sonra Total Nazal Semptom Skoru (TNSS), Oküler Yüzey Hastalık İndeksi (OYHI), Schirmer I testi ve gözyaşı kırılma zamanı (GYKZ) değerlendirilerek karşılaştırıldı. Tedaviden önce ve sonra göz içi basıncı (GİB) değerleri de ölçüldü. Çalışmaya, geriatrik popülasyondaki tüm rinit olguları (alerjik ve nonalerjik) dâhil edildi. **Bulgular:** TNSS, OYHI skoru, Schirmer ve GYKZ değerleri, nazal steroid (beklometazon dipropiyonat) tedavisinden sonra anlamlı derecede düzeldi ($p<0,001$). Sağ ve sol göz GİB değerlerinde anlamlı değişiklik saptanmadı (sırasıyla $p=0,608$; $p=0,062$). **Sonuç:** Önerilen dozlarda nazal steroid tedavisi; yaşlı erişkinlerde GİB'i etkilemeden, hem rinit hem de kuru göz semptomları için etkili olabilir, böylece kuru göz semptomları için birden fazla ilaca olan ihtiyacı azaltabilir. Çalışmamız, daha geniş serilerde tasarlanmış daha ileri çalışmalarla desteklenmelidir.

Anahtar Kelimeler: Kuru göz; nazal steroid; yaşlı erişkinler; rinit; Schirmer testi

Rhinitis is a common disease which can be seen in all age groups, mainly classified as allergic and non-allergic rhinitis (such as vasomotor rhinitis, senile rhinitis, hormonal rhinitis). Although most of the rhinitis cases seen in the geriatric population are senile rhinitis, all of the other types of

rhinitis are also observed.¹ Rhinitis (allergic and non-allergic) in the geriatric population is characterized as the rhinitis seen over 65 years old and most often presents as late-onset, bilateral watery nasal secretions without endonasal mucosal or anatomic pathology.¹

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Since intranasal corticosteroids are commonly used in the treatment of both allergic and non-allergic rhinitis (if there is no contraindication), further evaluations are not always necessary for the differential diagnosis.^{1,2}

Dry eye is a multifactorial disease affecting the tears and ocular surface. It results in discomfort, visual disturbance, and tear film instability possibly damaging the ocular surface, and in companion with increased tear film osmolarity and ocular surface inflammation.³ Dry eye primarily affects older adults and is prevalent among them, affecting up to 30% of adults aged ≥ 50 years.⁴ Most people with dry eye are over 65 years of age, and women are more likely to develop dry eye due to hormonal changes and menopause.⁴ Dry eye affects both visual function and quality of life.^{3,4} Patients who suffer from dry eye; complain of burning, aching, dryness, and foreign body sensation besides itchy, heavy, fatigued, and, red eyes with photophobia and blurred vision.^{3,4} In addition, dry eye can cause inflammation.^{3,4} Tests such as Schirmer I and tear break-up time (TBUT) are simple and useful tests, which are frequently used in the diagnosis of dry eye.^{3,4} Topical corticosteroids have a critical role in abating the inflammatory process in dry eye pathogenesis, but long-term steroid therapy can lead to complications such as increased intraocular pressure (IOP) and cataract formation.⁴

In our study, we evaluated the effect of nasal steroid treatment on both rhinitis and dry eye in rhinitis cases (allergic or non-allergic rhinitis) in the geriatric population.

MATERIAL AND METHODS

This retrospective, single-center clinical study was conducted at Health Sciences University, İzmir Tepecik Training and Research Hospital Department of Ophthalmology, with the collaboration of the Department of Otorhinolaryngology, between 1 October 2019 and 31 December 2019 and adhered to the tenets of the Declaration of Helsinki. Approval was received from the Health Sciences University İzmir Tepecik Health Practice Research Center Non-interventional Ethics Committee (No: 2019/13-25; Date: 11.9.2019) and written informed consent was obtained from all patients.

In our study, we did not define our patients as senile rhinitis in order to avoid diagnostic difficulties. Therefore, we included all rhinitis cases (allergic and non-allergic) in the geriatric population. Between 1 October 2019 and 31 December 2019, the following tests were performed in patients diagnosed with rhinitis and dry eye: Total Nasal Symptom Score (TNSS), Ocular Surface Disease Index (OSDI), Schirmer I, and TBUT tests. IOP was evaluated using a Goldmann applanation tonometer (Topcon, Japan) in the morning by the same doctor.

We included 31 patients over the age of 65 years who had dry eye symptoms and were using nasal steroids (beclomethasone dipropionate) due to rhinitis. Beclomethasone dipropionate was applied as 2 \times 2 puff (50 μ g) dose for 4 weeks. Symptoms and findings were compared before and after nasal steroid treatment. Patients with a high degree of nasal septum deviation limiting nasal steroid application, diffuse nasal polyposis, history or findings of nasal mass, and previous treatment with radiotherapy in the head and neck region were excluded. Patients who were on corticosteroids, nonsteroidal anti-inflammatory drugs, bronchodilators, mast cell stabilizers or were receiving photochemotherapy or immunosuppressant treatment within 3 months before inclusion in the study, were also excluded. Patients with a history of chronic contact lens use or eye surgery and receiving any treatment for dry eye were excluded.

TNSS, OSDI, Schirmer I and TBUT test results, and IOP values were compared pre- and post-treatment.

OTORHINOLARYNGOLOGIC ASSESSMENT

TNSS is a quick, easily applied, and well-tolerated self-report questionnaire and is used to evaluate symptoms and treatment outcomes of patients with rhinitis.⁵ It assesses symptom severity of nasal congestion, nasal itching, sneezing, and rhinorrhea of patients in the past week. Patients score each symptom from 0 to 3 (0: no complaints; 1: mild; 2: moderate; and 3: severe). The highest score was 12.

OPHTHALMOLOGIC ASSESSMENT FOR DRY EYE

In the Schirmer I test (without topical anesthesia), 35 mm long and 5 mm wide absorbent strips are used.

The strip is placed inside the inferior fornix. The patient closes his/her eyes during five minutes. After five minutes, the paper is removed, and the amount of moisture is evaluated. The results are defined as the wet length of the strip measured after five minutes. Amount of moisture ≤ 5 mm is considered as dry eye.³

For the TBUT test, a fluorescein dye was applied, and 2 minutes later, tear film is observed under cobalt blue illumination. The patient should blink once and then keep the eyes open. The TBUT is recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film. The test is repeated for 3 times, and the average is recorded. A TBUT test score of equal or lower than 10 seconds is considered as abnormal.³ A positive Schirmer I test or TBUT test, along with the presence of dry eye symptoms, was considered to indicate dry eye.³

To understand and evaluate the dry eye complaints of the patients, as well as the objective evaluation methods, we used assessing dry eye disease and evaluated the OSDI.

Assessing dry eye disease: The answers D and E were used in order to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the scheme below (Figure 1). We checked where the patient's score would correspond. To check if the patient's score remarks normal, mild, moderate or severe dry eye disease, we matched the corresponding shade of red with the key below (Figure 1).⁶

Ocular Surface Disease Index: OSDI is rated on a scale from 0 to 100, and higher scores represent more insufficiency. The index is both sensitive and specific to dry eye disease. It is an effective and a de-

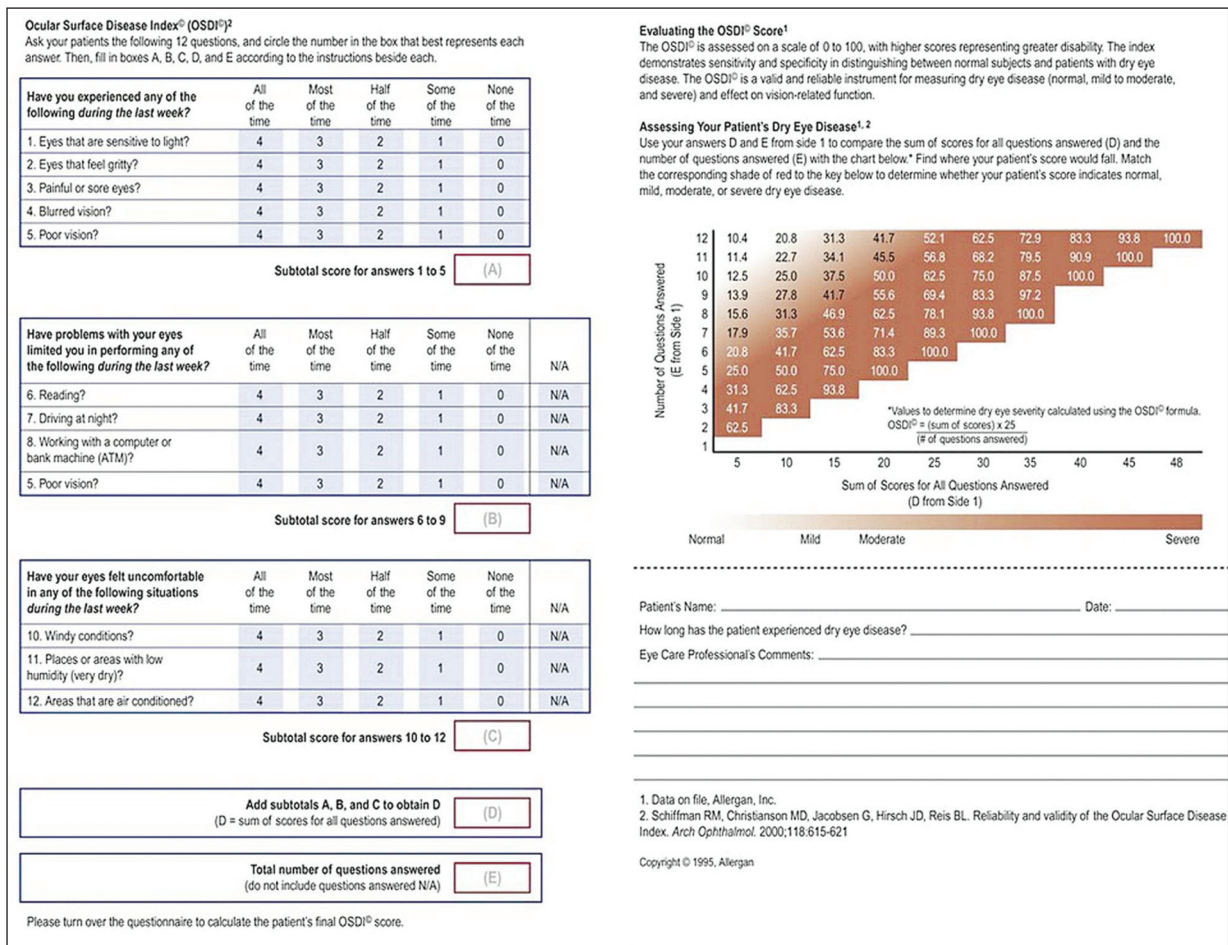


FIGURE 1: Ocular Surface Disease Index scores.

pendable tool for evaluating dry eye disease (normal, mild to moderate and severe) and its effect on visual function (Figure 1).⁷

STATISTICAL ANALYSIS

All the data were evaluated using IBM SPSS Statistics Standard Concurrent User V 25 (IBM Corp., Armonk, NY, USA) software. Descriptive statistics were presented as number (%) or as mean±standard deviation ($\bar{X}\pm SS$). The normality of the difference between the values of the patients before and after nasal steroid use was assessed with the Shapiro-Wilk normality test and *Q-Q* graphics. The statistical significance of the differences between pre-treatment and post-treatment values were evaluated with the paired t-test. Relationships between numerical variables were evaluated with Pearson correlation analysis. $p<0.05$ was considered statistically significant.

RESULTS

We included 31 patients. Of the patients, 6 (19.4%) were men and 25 (80.6%) were women. The age range was 65-75 years (mean age, 68.03 ± 3.17 years).

After the nasal steroid treatment, TNSS, OSDI, both Schirmer and TBUT values of both right and left eyes were statistically significantly different ($p<0.001$); however, there was no significant change in IOP values (Table 1).

Table 2 revealed that before the treatment, there was a weak negative correlation between TNSS and

Schirmer values in both eyes ($p=0.045$ $p=0.043$ respectively), a strong positive correlation between right and left eye Schirmer values ($p<0.001$), a moderate positive correlation between right eye Schirmer and TBUT values ($p=0.011$), and a moderate positive correlation between left eye Schirmer and TBUT values ($p=0.023$), a strong positive correlation between right and left eye TBUT values ($p<0.001$), a weak negative correlation between right eye TBUT values and left eye IOP values ($p=0.058$), and a strong positive correlation between right and left eye IOP values ($p<0.001$).

According to Table 3, after the treatment, there was a weak negative relation between TNSS and left eye Schirmer values ($p=0.049$), weak positive relation with left eye IOP values ($p=0.043$), and a moderate positive relation with OSDI scores ($p=0.001$), a strong positive correlation between right and left eye Schirmer values ($p<0.001$), a moderate positive correlation between right eye Schirmer, and TBUT values of both right and left eyes ($p=0.002$ $p=0.003$ respectively). Moreover, there was a moderate positive correlation between left eye Schirmer and right eye TBUT values ($p=0.001$), a strong positive correlation between left eye Schirmer and left eye TBUT values ($p<0.001$), a strong positive correlation between right and left eye TBUT values ($p<0.001$), and a strong correlation between right and left eye IOP values ($p<0.001$).

A moderate positive correlation between TNSS differences and OSDI differences was detected ($p=0.007$) (Table 4).

TABLE 1: Comparison of values of patients before and after nasal steroid treatment.

	Evaluation time		Test statistics	
	Before nasal steroid $\bar{X}\pm SS$	After nasal steroid $\bar{X}\pm SS$	t value	p value
TNSS	9.64±1.27	4.58±1.71	14.602	<0.001
Right eye Schirmer (mm)	8.74±6.24	14.38±6.76	7.069	<0.001
Left eye Schirmer (mm)	7.61±5.79	12.61±6.42	6.550	<0.001
Right eye TBUT (sec)	5.23±2.95	9.32±4.76	5.771	<0.001
Left eye TBUT (sec)	4.67±2.32	8.90±4.10	7.079	<0.001
Right eye IOP (mmHg)	17.83±2.09	17.67±2.39	0.518	0.608
Left eye IOP (mmHg)	18.22±2.41	17.64±2.41	1.937	0.062
OSDI	24.03±6.90	18.32±7.55	9.551	<0.001

SS: Standard deviation; TNSS: Total Nasal Symptom Score; TBUT: Tear break-up time; IOP: Intraocular pressure; OSDI: Ocular Surface Disease Index.

TABLE 2: Correlation of values of patients before nasal steroid treatment.

	TNSS	Right Schirmer (mm)	Left Schirmer (mm)	Right TBUT (sec)	Left TBUT (sec)	Right IOP (mmHg)	Left IOP (mmHg)
TNSS							
r value							
p value	-						
Right Schirmer (mm)							
r value	-0.363						
p value	0.045	-					
Left Schirmer (mm)							
r value	-0.366	0.663					
p value	0.043	<0.001	-				
Right TBUT (sec)							
r value	-0.172	0.448	0.265				
p value	0.354	0.011	0.150	-			
Left TBUT(sec)							
r value	-0.096	0.187	0.408	0.694			
p value	0.609	0.314	0.023	<0.001	-		
Right IOP (mmHg)							
r value	-0.072	-0.011	0.151	-0.365	-0.352		
p value	0.702	0.954	0.417	0.043	0.052	-	
Left IOP (mmHg)							
r value	-0.027	-0.151	0.056	-0.344	-0.306	0.868	
p value	0.885	0.419	0.763	0.058	0.094	<0.001	-
OSDI							
r value	-0.029	-0.035	-0.091	0.171	0.169	-0.158	-0.136
p value	0.878	0.850	0.628	0.356	0.365	0.395	0.465

TNSS: Total Nasal Symptom Score; TBUT: Tear break-up time; IOP: Intraocular pressure; OSDI: Ocular Surface Disease Index.

Our study results indicate that TNSS and OSDI scores decreased together; however, Schirmer and TBUT values increased after the treatment.

DISCUSSION

Official epidemiologic data on rhinitis in older people are restricted even though various changes definitely correlated with advancing age in the nose have been analyzed.¹ The prevalence of allergic rhinitis is rising among older adults however, non-allergic reasons might be more common with advancing age.⁸ Age-related physiologic changes like cholinergic hyperactivity and anatomic changes (atrophic structural changes in the connective tissues, mucosal glands, and nasal vasculature) might affect rhinitis in older adults. Drying and increased nasal congestion might be caused by these anatomic changes, increasing or

complicating other causes of rhinitis. Local atrophy, atrophic rhinitis and congestion may result from reduced blood flow to the nasal mucosa.⁸ Even though rhinitis in older adults may lead to mucosal dryness, these people are more likely to complain marked, clear rhinorrhea as a result of cholinergic hyperactivity.⁸ Intranasal corticosteroids are the most effective medications to control all rhinitis symptoms. They are generally safe, and side effects are generally mild (crusting, dryness, and minor epistaxis) and have an important role in the treatment of both dry eye disease and rhinitis.⁹

Dry eye affects 5-40% of adults >40 years.^{10,11} The incidence of dry eye disease increases with age, with as many as 10-25% of older adults being affected at some time.^{12,13} Women suffer from dry eye more than men.¹¹ Consistent with the literature, in our

TABLE 3: Correlation of values of patients after nasal steroid treatment.

	TNSS	Right Schirmer (mm)	Left Schirmer (mm)	Right TBUT (sec)	Left TBUT (sec)	Right IOP (mmHg)	Left IOP (mmHg)
TNSS							
r value							
p value	-						
Right Schirmer (mm)							
r value	-0.199						
p value	0.283	-					
Left Schirmer (mm)							
r value	-0.356	0.847					
p value	0.049	<0.001	-				
Right TBUT (sec)							
r value	-0.208	0.538	0.566				
p value	0.261	0.002	0.001	-			
Left TBUT (sec)							
r value	-0.230	0.516	0.682	0.865			
p value	0.214	0.003	<0.001	<0.001	-		
Right IOP (mmHg)							
r value	0.226	-0.185	-0.084	-0.288	-0.064		
p value	0.221	0.319	0.653	0.116	0.731	-	
Left IOP (mmHg)							
r value	0.367	-0.197	-0.140	-0.337	-0.118	0.836	
p value	0.043	0.287	0.452	0.064	0.527	<0.001	-
OSDI							
r value	0.553	0.097	0.022	-0.039	0.124	0.197	0.293
p value	0.001	0.602	0.907	0.834	0.507	0.288	0.109

TNSS: Total Nasal Symptom Score; TBUT: Tear break-up time; IOP: Intraocular pressure; OSDI: Ocular Surface Disease Index.

study, it was found out that 81% of the patients with dry eyes were women as well. Dry eye is one of the most common ophthalmic disorders, and causes ocular irritation, hyperemia, glare, eye fatigue and blurred vision. Increase in higher-order aberrations, and superficial punctate keratitis lead to vision deterioration in dry eye. In addition, blindness from corneal opacification or ulceration might be the results in some severe cases.¹⁴ In order to detect dry eye and evaluate its harshness, several clinical tests such as Schirmer test, TBUT, tear osmolarity, and vital dye staining of the cornea are used.^{3,4} Symptoms and signs may improve with treatment, in addition, symptom severity does not always correlate with the severity of signs on ophthalmologic evaluation.¹² Treatment goals are to improve the quality of life in terms of decreased symptoms and signs by reducing environmental causes and discontinuing medications

that may cause or worsen dry eye.^{12,13} The contribution of pro-inflammatory cytokines to dry eye pathogenesis has been recognized, and studies have been using anti-inflammatory drugs in the treatment of this disease, particularly corticosteroids, such as methylprednisolone and dexamethasone.^{4,15,16} However, because long-term use of steroid (both systemic and topical ophthalmic steroids) can cause complications such as increased IOP, and cataract formation, but their development depends on the duration and dose of treatment, so careful follow-up is necessary.^{6,17-19}

Nasal corticosteroids are widely practiced in the treatment of rhinitis.²⁰ Inhaler and nasal corticosteroids have minimal side effects in comparison with topical ophthalmic applied corticosteroids.¹⁷ They are absorbed through the nasal and oropharyngeal mucosa and reach the target tissue. They may enter the

TABLE 4: Correlation of differences of values before and after nasal steroid treatment.

	TNSS	Right Schirmer (mm)	Left Schirmer (mm)	Right TBUT (sec)	Left TBUT (sec)	Right IOP (mmHg)	Left IOP (mmHg)
TNSS							
r value							
p value	-						
Right Schirmer (mm)							
r value	0.036						
p value	0.847	-					
Left Schirmer (mm)							
r value	-0.126	0.621					
p value	0.500	<0.001	-				
Right TBUT (sec)							
r value	-0.073	0.742	0.405				
p value	0.695	<0.001	0.024	-			
Left TBUT (sec)							
r value	-0.034	0.745	0.616	0.762			
p value	0.856	<0.001	<0.001	<0.001	-		
Right IOP (mmHg)							
r value	-0.043	-0.021	-0.348	-0.022	-0.086		
p value	0.818	0.912	0.055	0.907	0.645	-	
Left IOP (mmHg)							
r value	0.019	-0.186	-0.099	-0.254	-0.174	0.738	-
p value	0.919	0.317	0.597	0.168	0.350	<0.001	
OSDI							
r value	0.475	-0.031	-0.113	-0.347	-0.112	0.170	0.349
p value	0.007	0.868	0.545	0.056	0.550	0.360	0.054

TNSS: Total Nasal Symptom Score; TBUT: Tear break-up time; IOP: Intraocular pressure; OSDI: Ocular Surface Disease Index.

systemic circulation in sufficient concentration and produce adverse effects.¹⁸

The corticosteroids have anti-inflammatory effect and also exert local immunomodulatory activity through inhibition of the activity of certain transcription factors. Clinical trials have shown the effectiveness of topical ophthalmic corticosteroid treatment in reducing symptom severity and lessening ocular surface staining. Unfortunately, the long-term use of topical or systemic corticosteroid is associated with detrimental negative effects; however, repetitive short-term pulse therapy with topical corticosteroids is not only an auspicious method for utilizing their beneficial effects but also reduces the risk of adverse events.^{21,22}

Yang et al. explained that; after additional steroid eye drops were applied to patients who had already

used artificial tears, all the patients showed fewer symptoms within a week the soonest. The mean value of the symptom score, TBUT, corneal fluorescein staining, and the Schirmer test I all improved significantly, and no significant difference was found in IOP.²³ Jung et al. analyzed the long-term outcome of topical loteprednol etabonate 0.5% or fluorometholone 0.1% treatment twice daily in patients with severe dry eye related with Sjögren's syndrome. Visual acuity, IOP, Schirmer test, TBUT, keratoepitheliopathy, and symptom scores were evaluated at baseline and 6, 12, 18, and 24 months after treatment. In none of the groups, visual acuity and IOP changed significantly during follow-up. Schirmer test results, keratoepitheliopathy, symptom scores, and TBUT at 12, 18, and 24 months significantly improved after treatment in both groups.²⁴

In the literature, there is no other study evaluating the effect of nasal steroid treatment on dry eye and IOP in older adults with both rhinitis and dry eyes. Yenigun et al. evaluated the effect of nasal steroid treatment on dry eye symptoms in patients with allergic rhinitis.²⁵ They found that dry eye symptoms remarkably improved with nasal steroid treatment, without affecting the IOP.²⁵ Our study results were consistent with theirs, in that the nasal steroid treatment led to a significant improvement in OSDI scores without affecting the IOP.²⁵ However, in contrast to their study, we noticed significant changes in Schirmer and TBUT values in both eyes. In our study, before treatment, both Schirmer and TBUT values were less than the values in their study, but after treatment, these values increased more than the values in their study. These differences may result from the differences in the mean age and the seriousness of dry eye between the two studies. Dry eye is a common problem in older adults.⁴ Thus, the treatment, even in low nasal steroid doses, may easily relieve dry eye symptoms.

In our study, we observed remarkable improvement in rhinitis symptoms and decrease in TNSS and OSDI values after the beclomethasone dipropionate treatment. In contrast with Yenigun et al.'s study, we noticed remarkable improvement in TNSS, OSDI, Schirmer, and TBUT values.²⁵ Moreover, we did not notice any side effects with nasal beclomethasone dipropionate after 4 weeks of treatment. These results provide a new insight into the treatment of older adults presenting with both rhinitis and dry eye. Glaucoma and cataract are usually detected in individuals over 40 years of age.⁴ Therefore, application of nasal steroid as a single medication to improve both rhinitis and dry eye, without affecting IOP, may be an effective treatment strategy.

Although the populations of our study and Yenigun's study are different, there is no other similar study with which to compare our results.²⁵ Our results indicate that older adults with concomitant rhinitis and dry eye may benefit from first-line nasal steroid treatment. If dry eye symptoms persist, other treatment options can be added.

Our study has some limitations. We did not include a control group. Moreover, we did not classify the rhinitis cases in older adults and did not determine the duration of rhinitis and dry eye. Lack of generalizability might have affected our study results. The patients were referred to the ophthalmology clinic from the otorhinolaryngology clinic, and nasal steroid treatment was discontinued in most patients with rhinitis at 3 months. Therefore, the study was conducted over a 3-month period and the effect of nasal steroid on dry eye symptoms and tests were evaluated for a 3-month period. That's why we could not evaluate the long term effect of nasal steroid treatment. Our results should be confirmed with further studies with larger sample size.

CONCLUSION

Our study is the first to emphasize the importance of the association of dry eye and rhinitis in older adults. Our data show that only 4-week nasal steroid treatment may significantly alleviate rhinitis and dry eye symptoms, as well as improving dry eye test results, in older adults. In addition, the treatment with nasal steroids at the recommended doses did not increase IOP. Polypharmacy tends to be common in older adults because of chronic diseases and aging; moreover, older adults have poorer hand-eye coordination, leading to difficulty in the instillation of eye drops. Therefore, treating both rhinitis and dry eye symptoms with only one medication, nasal steroids, may be a straightforward, efficient, and cost-effective solution, at least in the beginning of the treatment.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Esin Kırıkkaya, Engin Başer; **Design:** Esin Kırıkkaya, Engin Başer; **Control/Supervision:** Esin Kırıkkaya, Engin Başer; **Data Collection and/or Processing:** Esin Kırıkkaya,

Engin Başer; **Analysis and/or Interpretation:** Esin Kırıkkaya; **Literature Review:** Esin Kırıkkaya, Engin Başer; **Writing the Article:** Esin Kırıkkaya; **Critical Review:** Esin Kırıkkaya, Engin Başer.

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