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THE EFFECTS of PREGABALINE TREATMENT on BASAL TEARS RELEASE and TEARS FILM STABILITY in FIBROMYALGIA PATIENTS WITHOUT DRY EYE SYNDROME

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ABSTRACT

Introduction: To evaluate ocular surface disease index, basal secretion test and tear breakup time test of pregabalin treatment in patients with FM without dry eye syndrome.

Materials and Method: 66 patients who met the study criteria between December 2014 and December 2016 were included. OSDI (Ocular Surface Disease Index) questionnaire showing qualitatively dry eye presence and severity, Schirmer and tear breakup time (T-BUT) tests were administered to all patients included in the study before the start of pregabalin treatment, in the second week and the second month during treatment. Data of the radiological and clinical evaluations in preoperative and follow-up periods were compared statistically. Statistical significance was accepted at $p<0.05$.

Results: The mean age of all patients was 40.48±7.6 years. Mean age of the 12 males was 30.3±5.2 and 42.4±7.6 of the 44 females. OSDI scores averaged 18.83±8.23, 19.12±9.37, 19.06±12.78 for pre-treatment and after 2 weeks and 2 months of drug use, respectively. No significant statistical difference was found between these values ($p = 0.58$). The mean values of Schirmer test scores, pre-treatment, post-treatment second week and second months values were 17.46±3.5, 17.78±2, and 17.51±3.5, respectively, which were not statistically significant ($p = 0.76$). The mean values of t-BUT scores were 11.56±0.5, 11.45±0.5, 11.83±0.4 for pre-treatment and after 2 weeks and 2 weeks of treatment, respectively. Changes in t-BUT values were not statistically significant ($p = 0.62$).

Conclusion: The use of pregabalin is a safe and effective method for tear release in the treatment of patients with FM who have not received dry eye diagnosis before the age of 50 years.

KEYWORDS : pregabalin; fibromyalgia; dry eye syndrome; basal tear release;

INTRODUCTION

Dry eye syndrome is a multifactorial disease of the tear film and ocular surface that can result in ocular surface damage and visual impairment. Previous studies have shown a decrease in osmolarity of the tear film layer as a result of ocular surface inflammation in rheumatologic diseases (1).

Fibromyalgia (FM) is a syndrome with chronic widespread pain accompanied by fatigue, restless sleep and cognitive dysfunction (2), and it has been shown in previous studies that FM may be associated with other autoimmune syndromes that may lead to dry eye syndrome, as well as dry eye syndrome may develop in patients with FM alone (3,4).

FM, which is a rheumatologic disease characterized by widespread musculoskeletal pain, chronic widespread tension and / or stiffness in the joints and muscles, fatigue, functional and emotional disturbances, and pain sensation at sensitive points, is often associated with other rheumatic diseases (Sjogren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis).

Pregabalin is an alpha-2 delta subunit receptor ligand drug approved by the FDA (Food and Drug Administration) (5), which is frequently used in FM therapy. FM has been shown to reduce pain in many studies. However, a study evaluating the effect of pregabalin on the ocular surface has not yet been found in the literature (6,7).

The aim of this study was to evaluate ocular surface disease index, basal secretion test and tear breakup time test of pregabalin treatment in patients with FM without dry eye syndrome.

MATERIALS AND METHOD:

Between December 2014 and December 2016, 66 patients who met the study criteria who diagnosed with FM on our orthopedic clinic were included. The patients were newly diagnosed with FM but were untreated according to criteria that were established by the American College of Rheumatology in 1990 and were referred to the Ophthalmology Clinic.

As inclusion criteria, a single eye (right or left) of patients, who are under the age of 50 with a new FM diagnosis taken pregabalin treatment and without dry eye syndrome was included in the study. Those with Sjogren's syndrome and other rheumatologic diseases; thyroid disease, endocrine disease such as diabetes; eye disease other than dry eye (such as blepharitis); ocular and systemic infections; those who use any topical and systemic medicines; contact lens users and intraocular surgery patients were not included in the study.

OSDI (Ocular Surface Disease Index) questionnaire showing qualitatively dry eye presence and severity, Schirmer and tear breakup time (T-BUT) tests were administered to all patients included in the study before the start of pregabalin treatment, in the second week and the second month during treatment, three times in total. Symptoms of ocular irritation compatible with dry eye were evaluated by OSDI scoring system.

All the patients were informed of the study content and objectives, and the informed consent forms were obtained.

In statistical analyses, Statistical Package for Social Sciences (SPSS) software (version 21.0,SPSS Inc., Chicago, IL, USA) was used. The paired Student's t test was used to compare the preoperative and postoperative outcomes. Statistical significance was accepted at $p<0.05$.

Data of the clinical evaluations in preoperative and follow-up periods were compared statistically.

OSDI:

It consisted of 12 questions and three parts; ocular symptoms, visual function and environmental triggering factors. There were 5 questions in the first section, 4 questions in the second section, and 3 questions in the third section. Symptoms in each section were scored from 0 to 4 according to the frequency of feeling (0 = never, 4 = always). In the second and third sections, involving visual function and triggering factors, the answer was considered invalid if there is no factor triggering the symptom. In the OSDI survey, the scoring was based on the number of valid questions received. The OSDI score was determined by the equation of the total point x 25 / valid number of questions.

t-BUT test:
Fluorescein papers (Haag-Streit, Koeniz, Switzerland) were touched to the lower bulbar conjunctiva under the microscope. Without applying topical anesthesia, in the cobalt blue filter under the biomicroscope, in the area of the cornea, the time between the first breakup in the tear layer was measured with a chronometer in seconds after an exact blink and the average of the two measurements was taken. The t-BUT value was evaluated as dry eye under 10 seconds.

Schirmer Test:
After topical anesthesia with 0.5% proparaine hydrochloride (AlcaineR, Alcon), Schirmer papers (Optitech Eyecare, Allahabad, India) with a length of 30 mm was placed between 1/3 outer and 1/3 middle of lower eyelid fornix and after 5 minutes, the amount of wetting was recorded by measuring from the portion that coincide with the edge of the cap. Measurements below 5 mm were evaluated as dry eyes.

RESULTS:
The 66 patients who participated in the study were 12 male and 44 female. The mean age of all patients was 40.48±7.6 years. Mean age of the males was 30.3±5.2 and 42.4±7.6 of the females.

OSDI scores averaged 18.83±8.23, 19.12±9.37, 19.06±12.78 for pre-treatment and after 2 weeks and 2 months of drug use, respectively. No significant statistical difference was found between these values (p = 0.58) **(Table 2)**.

The mean values of Schirmer test scores, pre-treatment, post-treatment second week and second months values were 17.46±3.5, 17.78±2, and 17.51±3.5, respectively, which were not statistically significant (p = 0.76) **(Table 2).**

The mean values of t-BUT scores were 11.56±0.5, 11.45±0.5, 11.83±0.4 for pre-treatment and after 2 weeks and 2 weeks of treatment, respectively. Changes in t-BUT values were not statistically significant (p = 0.62), as were the other two test results **(Table 2).**

DISCUSSION:
The dry eye prevalence in the normal population ranges from 5.5 to 33.7%, whereas 45% for the over 65-year-old (8, 9). Lacrimal gland is target organ in autoimmune diseases. Inflammatory reactions cause impaired lacrimal gland function, resulting in reduced tear production (10). Deteriorated tear function tests suggest a possible pathophysiological link between FM and dry eye due to interference of immunological factors. Previous studies have found that 20% to 35% of dry eyes are present in patients with FM (11). Studies in patients with only FM diagnosed and dry eyes without accompanying additional diseases in the literature are rare. Previous studies investigating the relationship between dry eye and FM have used the Schirmer test, GKZ test and the relationship between corneal and conjunctival staining (4,12).

FM pain is known to be difficult to treat. In addition to pharma cological treatment, a multidisciplinary approach comes forward, which requires a combined approach of physical and cognitive interventions. Conventional analgesics are generally not effective. Antidepressants such as duloxetine and amitriptyline, antiepileptics such as gabapentin or pregabalin, and non-traditional analgesics are mostly used in therapy (13,14, 15) . Pregabalin is licensed for the treatment of epilepsy, generalized anxiety disorder and peripheral and central neuropathic pain in adults. In the USA and in some other countries, a license has been obtained for the treatment of FM. Pregabalin has a mechanism of action similar to gabapentin, binds to calcium channels and reduces calcium flux and affects GABAergic neurotransmission. It has antipyretic, analgesic and anxiolytic effects. Pregabalin is stronger than gabapentin due to its higher affinity for calcium channels and is therefore used at lower doses. It is suggested that pregabalin therapy may be initiated at a dose of 150 mg per day in the treatment of neuropathic pain. Based on the individual patient response and tolerability, the dosage may be increased to a dose of 300 mg per day after an interval of three to seven days and up to a maximum dose of 600 mg per day after an additional seven day interval if necessary. Since the effect of pregabalin administration on tear release is studied independently of the dose in our study, we think it is necessary to do further works to obtain dose-related data.

Patients who are already prone to tear quality deterioration due to FM become more susceptible to dry eye syndrome by using antidepressant, antihistamine, and anticholinergic drugs, which also reduce the tear production during the treatment process. This study was conducted to investigate the effect of pregabalin therapy on the tear release of FM patients without dry eye. In our study, we used the Schirmer test, GKZ, and OSDI to assess the tear release of patients in accordance with the literature.

OSDI is a questionnaire that allows rapid assessment of ocular surface symptoms associated with severity of illness, and the effect on the patient's visual function. OSDI makes a diagnosis of ocular surface disease easier, faster and more reliable. In our study, no correlation was found between OSDI score and diagnostic tests used for dry eye disease, tear breakup time, ocular surface staining pattern and basal secretion tests.

In a case-control study, it was reported that dry eye symptom was important for indication of FM severity, however, dry eye symptoms may occur after the treatments. In that study, abnormal Schirmer test scores were found in 19 (47.5%) of 40 patients and pathologic t-BUT was evaluated in 17 patients (42.5%) (12). However, the patients in a forementioned study were using antidepressant drugs known to affect tear production. In our study, patients were newly diagnosed FM patients and did not use any medicament before, which would affect their tear quality. There was no statistically significant difference in our study between OSDI score, the Schirmer test, and the t-BUT values the first measured, pre-treatment of pregabalin, and the post-treatment of the second week and the second month. Gunaydin and his colleagues reported that pregabalin had the effect on tear release. In our study, pregabalin, which can be used as antiepileptic in comparison with antidepressant drugs, is reported to have no effect on tear release.

We think that our study is a good evaluation to indicate that the short-term (2 months) use of pregabalin has not an effect on tear release for the reason that the patient population is relatively more. Furthermore, the effectiveness and reliability of the tear measurement and evaluation tests we use also increase dependability by adding strength to our work.

There were some restrictions on our work. Because our study included patients only under the age of 50, the effect of pregabalin on tear release can not be said to cover all age groups. In addition, since pregabalin was not evaluated in patients with FM who had dry eye disease, the effect on dry eye disease was not evaluated. The relationship between dry eye disease, which is relatively common with FM and pregabalin, which is frequently used in FM treatment, is an open issue in the next period.

Pregabalin, whose usage has increased in recent years in FM treatment and has high efficacy, did not cause significant changes in tear breakup time and ocular surface staining tests. In addition, pregabalin does not cause ocular symptoms that can be evaluated with OSDI.

CONCLUSION:
The use of pregabalin is a safe and effective method for tear release in the treatment of patients with FM who have not received dry eye diagnosis before the age of 50 years

Table 1. Demographic evaluation

Characteristics	N	Age+Sd
Patients	66	40.48±7.6
Male	12	30.3±5.2
Female	44	42.4±7.6

Table 2. Evaluation of tear status

Scale	Pretreatment	Second week	Second Month
OSDI	18.83±8.23	19.12±9.37	19.06±12.78
t-BUP	11.56±0.5	11.45±0.5	11.83±0.4
Schirmer	17.46±3.5	17.78±2	17.51±3.5

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