

Effect of Tibolone Therapy on Postmenopausal Ocular Surface and Eye Symptomatology

TİBOLONE TEDAVİSİNİN POSTMENOPAZAL OKÜLER YÜZEY VE GÖZ SEMPTOMATOLOJİSİ ÜZERİNE ETKİLERİ

Selman LAÇİN*, Esin ERKİN**, Peyker TÜRKDOĞAN***, Aydın İŞİSAĞ***, Faik KOYUNCU*

* Dr, Dept. of Obstetrics and Gynecology, Medical School of Celal Bayar University,

** Dr, Dept. of Ophthalmology, Medical School of Celal Bayar University,

*** Dr, Dept. of Pathology, Medical School of Celal Bayar University, Manisa/TURKEY

Summary

Objective: To evaluate the effect of hormone replacement therapy on various clinical ocular parameters and cytological indices of conjunctival mucosa in women using tibolone.

Materials and Methods: In this prospective study, we took mucosal smears from the temporal conjunctiva of 26 postmenopausal women using tibolone before and at the end of third month of therapy. After fixation and Papanicolaou staining, cytology scores for each specimen based on the differential morphology were observed. In addition, ocular symptomatology were recorded and tear functions were evaluated by using Schirmer's, Rose Bengal's and Tear Break-up Time tests. Data were analysed using the Wilcoxon matched pairs rank sum test.

Results: We did not find a difference in cytology scores before and after therapy with tibolone but the tests related to amount and functions of tear showed a significant difference with therapy ($p<0.05$) and symptomatology related to eye complaints decreased significantly ($p<0.05$).

Conclusion: Our data support that hormone replacement therapy with tibolone has positive effect on ocular surface, increases the tear production and promotes ocular symptomatology in postmenopausal women.

Key Words: Tibolone, Tear function, Eye symptoms

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Özet

Amaç: Tibolone kullanan kadınlarda hormon replasman tedavisinin çeşitli klinik oküler parametreler ve konjonktival mukozanın sitolojik indeksleri üzerindeki etkisini araştırmak.

Materyel ve Metod: Bu prospektif çalışmada 2,5 mg/gün süreklili tibolone kullanan 26 kadının temporal konjonktivasından 3 aylık tedavi öncesinde ve sonrasında mukozal smear aldık. Bu smearlerde sitoloji skorlaması yapıldı. Ek olarak oküler semptomatoloji dolduruldu ve gözyaşı fonksiyonları Schirmer, Rose Bengal ve Gözyaşı kırılma zamanı tayiniyle değerlendirildi.

Bulgular: Tedavi öncesi ve sonrası konjonktival sitoloji skorlarında istatistiksel anlamlı bir fark bulamadık fakat gözyaşı miktar ve kalitesini ilgilendiren testlerde belirgin düzleme sağlandığı görüldü ($p<0.05$). Ayrıca oküler semptomlarda da iyileşme tespit edildi ($p<0.05$).

Sonuç: Verilerimiz tibolone ile yapılan hormon replasman tedavisinin oküler yüzey üzerine pozitif etkileri olduğunu, gözyaşı üretimini artırdığını ve göz semptomatolojisini düzelttiğini desteklemektedir.

Anahtar Kelimeler: Tibolone, Gözyaşı fonksiyonları, Oküler semptomlar

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Hormone replacement therapy (HRT), given mainly as estrogens and progestones, effects many organ systems. It has been shown that they significantly decrease bone turnover and prevent osteoporosis, and their use has been found to be associated with a decreased risk of coronary

heart disease (1-4). Nervous system and skin are other examples of target tissues where hormones may exert their beneficial effects (5-6).

Many epidemiological studies also indicate an increased incidence of certain vision-threatening conditions in postmenopausal women (7-8). These data suggest that changes in sex steroid levels may effect the physiology of eye and cause appearance of some ocular symptoms ranging from burning sensation to pain and even various degrees of visual loss. Low hormone levels seem to make the eye more susceptible to aqueous deficiency and squamous

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Yazışma Adresi: Dr.Selman LAÇİN
Celal Bayar Üniversitesi Tıp Fakültesi
Kadın Hastalıkları ve Doğum AD, MANİSA

metaplasia, which may be important especially in keratoconjunctivitis sicca and other "dry-eye" problems.

Hormone replacement therapy given to prevent from the adverse affects of postmenopausal syndrome has been shown to reduce the incidence of these eye-related diseases by different authors (9-10). In our knowledge, there is no data in the literature about the vision symptomatology and eye-related diseases while using tibolone, a synthetic steroid related to norethisterone, which has weak estrogenic, progestogenic and androgenic properties. It is a relatively new oral compound used for postmenopausal symptoms and for prevention of osteoporosis without causing endometrial and breast stimulation (11).

In this prospective study, we evaluated the effect of hormone replacement therapy on tear function by different tests, cytological changes in conjunctival mucosa as a hormone sensitive epithelium and eye symptomatology in postmenopausal women using tibolone.

Materials and Methods

The study protocol was approved by the Research Ethics Committee of Medical School of Celal Bayar University, and all subjects provided written informed consent prior to study. Thirty healthy postmenopausal women, ages evenly distributed from 46-61 years, were included into the study from the Menopause Unit of our University Outpatient Clinic. They were all undergone spontaneous menopause at least for 1 year previously confirmed by elevated gonadotropins and low estradiol levels. None of the subjects had received any form of HRT for at least 6 months prior to the beginning of the study. They were non-smokers, not receiving any medications which could be effective on ocular physiology and had normal renal, hepatic and thyroid functions. Patients with disorders that could cause ophthalmic impairment such as diabetes or chronic hypertension were also excluded.

Women enrolled into the study were evaluated in the Ophthalmology Department by the same ophthalmologist before and after three months of tibolone treatment (2,5 mg/day, continuously). The following tests were performed in order: Shirmer's test, tear break-up time, Rose Bengal staining test and conjunctival cytology. In addition, ocular symptoms were recorded by using an interviewer-administered questionnaire (Table 1). Ocular symptom score for each case was determined by counting the total number of eye symptoms in the questionnaire form.

Schirmer's test is a simple and objective evaluation of basal and evoked response of tear production and based on measurement of wet area in millimeters on a paper strip. It was done by placing the folded end of paper strips gently over the lower palpebral conjunctiva at its lateral one-third. After five minutes, the strips were removed and the amount of wetting was measured from the folded end. While this gives only a rough measurement, it is a valid indicator of lacrimal secretion at the clinical level (12).

Table 1. Patient Questionnaire

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1. Do you have problems in your vision?
 2. Do you experience dryness of the eyes?
 3. Do you have burning sensation of your eyes?
 4. Do you have photophobia?
 5. Do you experience intermittent blurring of your vision?
 6. Do you have tearing in your eyes?
 7. Do you experience tiredness around your eyes?
 8. Do you have puffy eyelids?
 9. Do you experience itching of your eyes?
 10. Do your eyelids get stuck to each other?
 11. Do you experience foreign body sensation in your eyes?
 12. Do you have mattering of your eyes?
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Break-up time test was performed without any anesthetic drops by using fluorescein paper sticks and cobalt blue filter of the slit lamp. While the patient refrained from blinking, the first dry spot appearing was noted in seconds. The average of three consecutive measurements was noted. It is an objective evaluation of stability of the tear film.

Another test that we used to show the hormone effect on conjunctiva was "Rose Bengal" dye test. It demonstrates devitalised cells by evaluating the average colour density on three different areas of conjunctiva. Rose Bengal scores using paper strips were evaluated by assessing staining in the interpalpebral space of the nasal and temporal bulber conjunctiva and of the cornea by using a scale between 0-3. The sum of staining scores in each of these three parts was used to determine the RB staining score for that eye.

Cytological specimens from the conjunctiva were collected with the cytobrush technique (13). After topical anesthesia, sterile cervical cytology brush (Oribrush Cell Collector, Orifice Medical, Sweden) was rotated a few times around itself on the inferotemporal bulber conjunctiva of both eyes while the patient was looking up and medially. The brush was rotated several times over a clean glass slide; it was fixated with 95% concentrated ethyl alcohol and stained with haematoxyline eosine. Cytological specimens were examined in the Pathology Department under light microscopy. Cell grading was done in a representative area by counting 100 cells and calculating the average number obtained by two different pathologists in a blinded fashion and applying the scheme modified from Nelson et al (14).

Grading System

Grade 1 (normal cytology): The epithelial cells are small and round with eosinophilic-staining cytoplasm. The nuclei have nucleocytoplasmic (N/S) ratio of 1/1-1/2. The goblet cells are abundant (a couple or more in each field), plump and have wide cytoplasm and abundant mucin.

Grade 2 (immature squamous metaplasia): The epithelial cells are slightly larger and more polygonal, and have

eosinophilic-staining cytoplasm . N/S ratio is 1/3-1/4. The goblet cells are fewer in number (1 or 2 in a couple of wide examination fields), however they still maintain the same morphology and mucin contents as Grade 1.

Grade 3 (immature squamous metaplasia): The epithelial cells are larger and more polygonal; the cytoplasm is fainter eosinophilic-staining. N/S ratio is 1/5-1/6. Goblet cells are rare (a few in the entire specimen) and smaller with poorly defined cellular borders, and have less mucin content.

Grade 4 (squamous metaplasia): The epithelial cells are large and polygonal with basophilic-staining cytoplasm. The nuclei is pycnotic or totally absent (N/S: 1/8). Goblet cells are totally absent.

Data were analysed using the Wilcoxon matched pairs rank sum test. Values except patient characteristics are expressed as standard error of mean (SEM). Statistical Package for Social Sciences (SPSS) software on an IBM personal computer was used for calculations. Significance was considered as $p < 0.05$.

Results

Twenty-six patients concluded the study; four women discontinued the medication (13%) because of some side effects (bleeding and breast tenderness) and poor compliance. The average age, body mass index and time between unset of menopause and enrolling the study of our population is shown in Table 2. We could not demonstrate a difference in conjunctival cytology scores before (1.88 ± 0.12) and after (2.11 ± 0.16) treatment with tibolone ($p = 0.13$) but the symptomatology scale related to eye complaints decreased significantly from 4.84 ± 0.19 to 2.57 ± 0.37 ($p < 0.05$) (Figure 1). Tests related to amount and quality of tear also showed a significant improvement with therapy. Shirmers test was changed from 19.19 ± 1.87 to 22.23 ± 1.87 seconds ($p < 0.05$) (Figure 2). Rose Bengal test was changed from 2.86 ± 0.19 to 2.11 ± 0.15 ($p < 0.001$) (Figure 3) and Tear Break-up time score was increased from 13.19 ± 1.4 to 17.88 ± 1.4 seconds ($p < 0.005$) (Figure 4).

Discussion

It is well known that both reproductive and buccal mucosa responds to fluctuations in estrogen and progesterone levels through maturational changes in their surface epithelium (15-16). Mature surfaces are characterised by a preponderance of superficial cells, representing a hyperestrogenic state where as immature epithelial surfaces are characterised by parabasal and intermediate cells representing a hypoestrogenic state. Postmenopausal period is characterised by low estrogen levels and atrophy of cells that are sensitive to these steroid hormones like vaginal epithelium and urothelium.

In conjunctiva, mature epithelium (transition from non-keratinised stratified cuboidal epithelium to squamous near the corneal limbus) is required for optimal film tear

Table 2. Characteristics of study population

Variables	
Age (years)	49.34±6,12 (46-61)
BMI (kg/m ²)	24,2±0,41
Years after menopause	4,1±3,25

Values are mean ± standard deviation, BMI: Body mass index

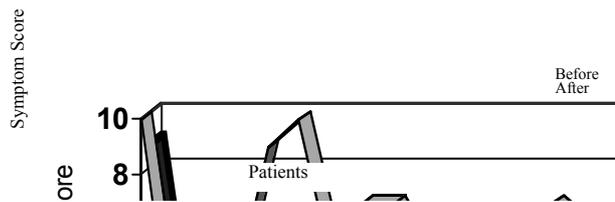


Figure 1. Eye-related symptoms before and after therapy with tibolone.

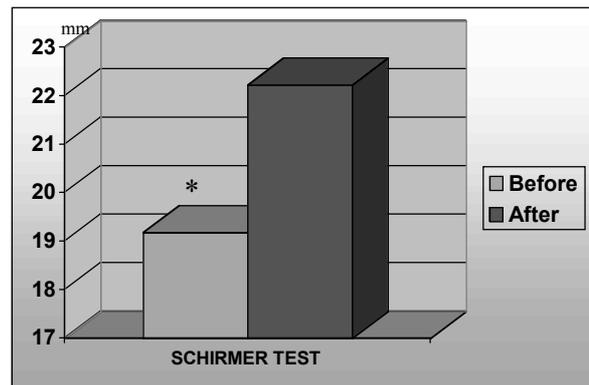


Figure 2. Schirmer's test before and after tibolone therapy. * $p < 0.05$.

production. Also adequate mucin production by goblet cells providing a smooth surface for the tear and some lipid production to prevent evaporation of the tear are required (17). Tibolone has been shown effective on genital epithelial maturation by its estrogenic properties (18-19). On the other hand, different authors have demonstrated that also conjunctiva is an estrogen sensitive epithelium (17,20). While the term "maturation" means a positive effect of estrogen in vaginal and ectocervical mucosa, it reflects an clinically undesirable condition for conjunctival epithelium since high conjunctival cytology scores are indicative of squamous metaplasia and "dry-eye" states. Hence, conjunctival cytology score, which we used in this study, is different from the classical papanicolau smears for evaluating the maturation

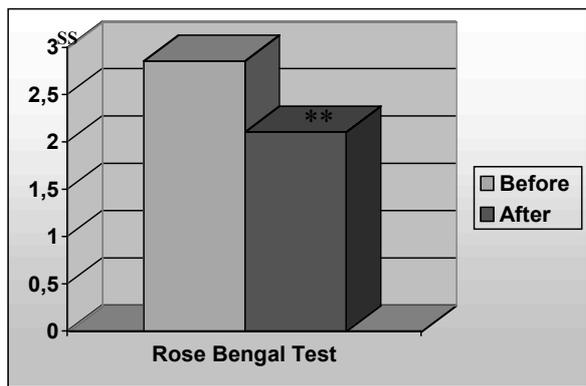


Figure 3. Rose Bengal Dye test before and after therapy with tibolone. **: $p < 0.001$, SS: Staining Score

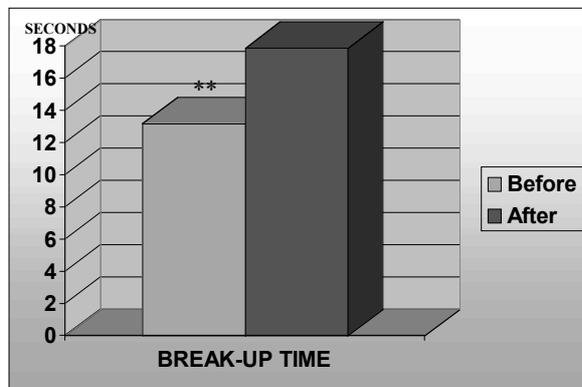


Figure 4. Tear Break-up Time before and after tibolone therapy. **: $p < 0.005$

indices in estrogen sensitive mucosal surfaces like vagina or cervix. We think that a slight and non-significant increase in conjunctival cytology scores we observed, was due to mixed hormonal effect of the compound; combined estrogenic, androgenic and progestogenic properties. At least, we can conclude that no adverse effects on conjunctival epithelium was observed.

From the clinical point of view, this mixed hormonal effect provided a significant improvement on the frequency and severity of postmenopausal eye complaints. Metka et al also (21) have found that eye-related symptoms were noted less frequently with estrogen and progesterone substitution. We believe that this decrease in symptoms were not only related with the quantity of tear but also with the stimulation of receptors located in different areas in eye. Gans et al (22) could not show estrogen and progesterone receptors in human conjunctiva by using monoclonal antibodies but more recently Ogueta et al (23) demonstrated estrogen receptor- α mRNA expression in retina, iris and retinal pigment epithelium of young females but not postmenopausal patients.

They concluded that sex steroid axis might play role in the pathogenesis of certain ocular diseases. Interestingly, androgens were reported to elevate a secretory component in the tears produced by the lacrimal gland of rats whereas estrogen showed no elevation (24-25). So, androgenic component of tibolone possibly can play a role in lacrimal secretion.

One may argue that improvement of eye-related complaints could be the result of placebo effect, not due to the drug itself since our study is not a placebo-controlled, randomized study. Although this is true, the improvements in different objective clinical tests support the results we obtained.

Both Schirmer's test and tear break-up time test showing the quantity and the stability of tear displayed a significant improvement in our study. Rose Bengal dye test also showed an objective decrease in the number of devitalised cells with tibolone therapy. All these tests are among the most preferred clinical diagnostic tests by ophthalmologist today.

Although our study period is rather short, this is the first study in the literature reporting an objective clinical evaluation of tibolone as HRT on tear quality and quantity and eye symptomatology. Tibolone as HRT is being prescribed by physicians in an increasingly manner because of its similar effects as other forms of HRT. Improvement of tear function and eye-related symptomatology seems another beneficial effect for the postmenopausal women to consider HRT with tibolone.

REFERENCES

- Orhaner S, Ezgü F, Varol F, Pekdemir S, Sevinç E, Yardım T. Postmenopozal Östrojen Replasmanının Osteoporozu Önlemedeki Etkisi. *Trakya Üniversitesi Tıp Fakültesi Dergisi* 1991-1993; (8-9-10): 325-33.
- Stampfer MJ, Colditz GA, Willett WC. Et al Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' health Study. *N Eng J Med* 1991; 325: 756-62.
- Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Int Med* 1991; 151: 75-80.
- Çengel A. Menopoz ve Kardiyovasküler Hastalık Riski. *Kardiyoloji* 1995; 2 (2): 142-4.
- Funk JL, Mortel KF, Meyer JS. Effects of estrogen replacement therapy on cerebral perfusion and cognition among postmenopausal women. *Dementia* 1991; 2: 268-72.
- Dunn LB, Damesyn M, Moore AA, Reuben DB, Greendale GA. Does estrogen prevent skin aging? Results from the First National Nutrition and health Examination Survey (NHANES I) *Arch Dermatol* 1997; 133: 339-44.
- Klein B, Klein R, Linton KLP. Prevalence of age related lens opacities in a population: The Beaver Dam Eye Study. *Ophthalmology* 1992; 99: 546-52.
- Mathers WD, Stovall D, Lane JA, Zimmerman MB, Johnson S. Menopause and tear function: the influence of prolactin and sex hormones on human tear production. *Cornea* 1998; 17 (4): 353-8.

9. Smith W, Mitchell P, Wang JJ. Gender, estrogen hormone replacement and age-related macular degeneration: results from the Blue Mountains Eye Study. *Aust N Z Ophthalmol* 1997; 25 (1): 13-5.
10. Benitez Del Castillo JM, Del Rio D, Garcia-Sanchez J. Effects of estrogen use on lens transmittance in postmenopausal women. *Ophthalmology* 1997; 104: 970-3.
11. Albertazzi P, Di Micco R, Zanardi E. Tibolone: a review. *Maturitas* 1998; 30(3): 295-305.
12. Puderbach S, Stolze H. Tear ferning and other lacrimal tests in normal persons of different ages. *Int Ophthalmol* 1991; 15: 391-5.
13. Anagnostopoulou-Fotiniopoulou I, Rammou-Kinia R. Cytobrush sampling in conjunctival cytology. *Diagn Cytopathol*. 1993; 9: 113-5.
14. Nelson DJ, Havener VR, Cameron DJ. Cellulose acetate impressions on the ocular surface: dry eye states. *Arch Ophthalmol* 1983; 101: 1869-72.
15. Main DMG, Ritchie GM. Cyclic changes in oral smears from young menstruating women. *Br J Dermatol* 1977; 79: 23-30.
16. Budak K, Kavur A, Gündüz K, Zilelioğlu G, Mızrak B, Ekinci C. Postmenopozal Kadınlarda Konjonktival İmpresyon Sitolojisi. *Oftalmoloji* 1995; 2 (1): 78-81.
17. Kramer P, Lubkin V, Potter V, Jacops M, Labay G, Silverman P. Cyclical changes in conjunctival smears from menstruating females. *Ophthalmology* 1990; 97: 303-7.
18. Rymer J, Chapman MG, Fogelman I, Wilson PO. A study of the effect of tibolone on the vagina in postmenopausal women. *Maturitas* 1994; 18 (2): 127-33.
19. Morris EP, Wilson PO, Robinson J, Rymer JM. Long term effects of tibolone on the genital tract in postmenopausal women. *Br J Obstet Gynaecol* 1999; 106(9): 954-9.
20. Vavilis D, Maloutas S, Nasioutziki M, Boni E, Bontis J. Conjunctiva is an estrogen-sensitive epithelium. *Acta Obstet Gynecol Scand* 1995; 74: 799-802.
21. Metka M, Enzelsberger H, Knogler W, Schurz B, Aichamair H. Ophthalmic complaints as a climacteric symptom. *Maturitas* 1991; 14: 3-8.
22. Gans LA, Lee SF, Lemp MA, Pepose JS. Estrogen and progesterone receptors and human conjunctiva. *Am J Ophthalmol* 1990; 109: 474-7.
23. Ogueta SB, Schwatz SD, Yamashita CK, Farber DB. Estrogen receptor in the human eye: influence of gender and age on gene expression. *Invest Ophthalmol Vis Sci* 1999; 40: 1906-11.
24. Sullivan D, Kelleher R, Vaerman J et al. Androgen regulation of secretory component synthesis by lacrimal gland acinar cells in vitro. *J Immunology* 1990; 145: 4238-44.
25. Cornell Bell A, Sullivan D, Allansmith M. Gender differences in the morphology of the lacrimal gland. *Invest Ophthalm & Vis Sci* 1985; 26: 1170-5.