

REVIEW

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Regarding the Dissertation for the Award of the Educational and Scientific Degree "Doctor"

in the Field of Higher Education 7. Health and Sports, Professional Field 7.1. Medicine,

Doctoral Program "Ophthalmology"

by Dr. Neli Krăsteva Nikolova-Petkova

on the Topic: "BIOLOGICAL THERAPY OF THE ANTERIOR OCULAR SURFACE, A STEP

TOWARDS PERSONALIZED OPHTHALMOLOGY"

The presented set of materials in both paper and electronic format is in compliance with the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria (ZDARSB) and the Regulations for the Development of Academic Staff at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

Brief Biographical Information

Dr. Neli Nikolova-Petkova graduated in Medicine from the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna in 2011. From 2012 to 2014, she worked as a medical representative. From 2013 to 2017, she specialized in ophthalmology at SBOBAL-Varna, and in 2017, after passing the exam, she obtained the specialty in "Ophthalmology." Since 2018, she has been working as a specialist doctor in ophthalmology at SBOBAL - Varna. After winning a competition in 2019, she was enrolled in the regular PhD program at the Department of Ophthalmology and Visual Sciences at MU-Varna. As a PhD student and a resident, Dr. Nikolova-Petkova has actively participated in both scientific research and clinical work. Since 2023, she has been working as an assistant at the Department of Optometry and Professional Diseases, MU-Varna. Her scientific interests focus on the anterior segment of the eye, surgical treatment of the anterior segment and ocular appendages, treatment and monitoring of patients with glaucoma, and aesthetic surgery. Dr. Nikolova continuously improves her qualifications

by attending courses and conferences every year, including "Aesthetic Facial Surgery," 2016, "Ocular Transplantation," 2017, "Multifocal Lens Fitting Course," 2019, "Modern Methods for Examining Structural Changes in the Retina (FAF and OCT)," 2019, "Lasers in Ophthalmology – Treatment of Eye Diseases," 2019, "Surgery of the Vitreous Body and Retina," 2020, "Ultrasound Diagnosis in Ophthalmology," 2020, "Amniotic Membrane," 2020, "Intravitreal Drug Administration," 2020, "Strabology," 2020. She is a member of the Bulgarian Medical Association and the Bulgarian Ophthalmological Society. She is fluent in English and has excellent computer skills.

The topic of the presented dissertation is relevant and suitable for dissertation.

Structure of the Dissertation

The presented dissertation is written on 228 pages and is in the form and volume that meets the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria (ZRASRB) and the Regulations of MU-Varna. The work is illustrated with 12 tables and 52 figures. It includes the following chapters:

- **Introduction** (3 pages)
- **Literature Review** (91 pages)
- **Aim and Objectives** (1 page)
- **Materials and Methods** (13 pages)
- **Results** (40 pages)
- **Discussion** (41 pages)
- **Conclusions** (2 pages)
- **Contributions** (1 page)
- **List of Publications Related to the Dissertation** (1 page)
- **References** (17 pages)

The bibliographic reference includes 176 sources in Latin script.

Literature Review

The literature review is very comprehensive. It covers the anatomy of the structures forming the anterior ocular surface (AOS), as well as the invasive and non-invasive diagnostic

methods for diseases of the AOS. Special attention is given to the tear film and its role in the protection, lubrication, and trophism of the structures in the anterior segments of the eye. The characteristics of various bioactive growth factors as components of the tear film and their role in reparative processes are described in detail. Particular focus is given to persistent epithelial defects, including their etiology, diagnostic methods, stepwise approach to treatment, treatment of refractory cases, and new therapeutic approaches. An interesting part of the work is the discussion of different types of ocular surface staining and data from the analyses, as well as the scales for assessing the stains and their diagnostic significance. The dissertation places particular emphasis on autologous serum drops, including their history, composition, production, application systems, advantages, and disadvantages. New therapeutic approaches are also thoroughly reviewed. Based on the literature review, five conclusions are drawn, which highlight the necessity of the research conducted in the dissertation.

Conclusions from the Literature Review:

- 1. There is a lack of data in Bulgaria on the evaluation and classification of various ocular diseases and the mechanisms of action that can lead to persistent epithelial defects.*
- 2. On a global scale, there is no assessment of subjective symptoms in patients with persistent epithelial defects.*
- 3. In Bulgaria, there is no assessment of different therapeutic approaches for ocular conditions related to persistent epithelial defects.*
- 4. Globally, no unified chart is found for evaluating objective and subjective signs in patients with persistent epithelial defects.*
- 5. There is no literature data on a standardized protocol for the preparation and use of autologous serum drops.*

Aim

The aim of the dissertation is to perform a detailed analysis of a wide range of ocular diseases characterized by persistent epithelial defects and to evaluate the clinical effectiveness of the applied therapeutic approaches.

Tasks to Achieve the Objective

To achieve this aim, the author has set six tasks:

1. *To conduct a review of the literature and evaluate the current diagnostic approaches for conditions associated with persistent epithelial defects, as well as the therapeutic approaches applicable to them.*
2. *To assess the etiology of diseases characterized by persistent epithelial defects in patients treated at the University Hospital of Ophthalmology and Eye Diseases (USBOBAL) in Varna.*
3. *To analyze the microstructural changes in the cornea in patients with persistent epithelial defects using in vivo confocal microscopy (Heidelberg Retina Tomograph II Rostock Cornea Module (HRT II-RCM)) and anterior segment optical coherence tomography (Cirrus HD-OCT 5000, Carl Zeiss Meditec, Inc).*
4. *To compare the results of the effectiveness of the treatment provided.*
5. *To assess the subjective symptoms and visual function in patients with persistent epithelial defects before and after treatment.*
6. *To create a map for the evaluation of the subjective and objective signs of patients with persistent epithelial defects, which will optimize the therapeutic approach.*

Methodology

The dissertation is based on a study conducted over a period of four years, from 01.12.2017 to 01.12.2021, at the University Hospital of Ophthalmology and Eye Diseases (USBOBAL) in Varna. A total of 102 patients were included in the study, all of whom were treated at the hospital, met the inclusion/exclusion criteria, provided informed consent, and had previously tested negative for hepatitis B, hepatitis C, syphilis, and HIV.

The study utilized several research methods:

1. **Documentary Method:** *To analyze patient records and previous clinical data.*
2. **Clinical Evaluation:** *Including visual acuity testing, subjective symptom assessment (irritation, pain, redness, foreign body sensation) based on a questionnaire, biomicroscopy of the anterior ocular surface, and advanced imaging techniques (anterior segment optical coherence tomography, in vivo confocal microscopy).*
3. **Therapeutic Methods:** *Based on the severity and etiology of the epithelial defect, the presence or absence of infiltrates, and the required treatment protocols.*

4. **Statistical Methods:** *To assess the outcomes and effectiveness of the various therapeutic approaches.*

Patients were divided into four treatment groups based on the etiology, size, depth of the epithelial defect, and the presence of an infiltrate:

- **Group I:** *Therapeutic Contact Lens (TCL)*
- **Group II:** *TCL + Autologous Serum Eye Drops (ASED)*
- **Group III:** *Amniotic Membrane (AM) + TCL + ASED*
- **Group IV:** *AM + ASED + TCL + Cross-Linking (in cases with infiltrate)*

For some of the patients, autologous serum eye drops were prepared following the standard operative protocol by Geerling and colleagues.

The surgical methods used in the study included:

- **Amniotic Membrane Transplantation:** *Applied as part of the treatment approach for patients with persistent epithelial defects.*
- **Corneal Cross-Linking:** *In cases where infiltrates were present, cross-linking was used to enhance the structural integrity of the cornea.*

This approach allowed for an in-depth assessment of the clinical effectiveness of the treatments, providing valuable data on the management of persistent epithelial defects in the anterior segment of the eye.

Results

The results obtained from the study are presented in an appropriate format, illustrated with numerous figures and tables. These results include evaluations of subjective symptoms such as pain, redness, foreign body sensation, as well as the size of the epithelial defect, conjunctival and ciliary injection, and the dynamics of visual acuity before and after treatment. The effectiveness of the treatment was assessed, along with data from anterior segment optical coherence tomography (AS-OCT) and in vivo confocal microscopy. Evaluations were made before the treatment, in the first and second weeks, and 30 days after the treatment began.

Regarding subjective symptoms, positive effects were observed as early as the first week, with 63.7% of patients reporting no pain, and by the first month, 86.3% were pain-free.

Statistically significant differences were found in pain perception among patients with different underlying etiologies leading to persistent epithelial defects (PED). The most pronounced effects were observed in patients with keratitis, trauma, burns, and foreign bodies. Regarding redness, it is notable that there was no severe redness as early as the first week, and a white eye effect was more pronounced at one month.

In terms of objective signs (size of the epithelial defect, conjunctival and ciliary injection, and visual acuity), similar improvements were observed.

The patients were randomized into four groups based on the assessment of subjective symptoms and objective findings:

- **Group 1:** *Patients with superficial epithelial defects without involvement of the corneal stroma were treated conservatively (58.4% of patients).*
- **Group 2:** *In patients with ulceration (stromal involvement without infiltrate), amniotic membrane transplantation (AMT) and therapeutic contact lenses (TCL) were performed, combined with 20% autologous serum eye drops (ASED) after the 7th day.*
- **Group 3:** *In patients (16.7% of the sample) with corneal infiltrates, PACK-CXL was performed, followed by AM and TCL, and after one week, 20% ASED was administered. Out of the clinical sample, 58.8% of patients underwent conservative treatment, while 42.1% required surgical treatment.*

An exceptionally interesting part of the study is the evaluation of the corneal characteristics in different etiological diseases obtained from the high-specialized tests (AS-OCT and in vivo confocal microscopy), as well as the assessment of the limbal epithelial thickness in the four quadrants according to the etiology and the density of the long nerves and sub-basal nerve plexus.

In the "Discussion" chapter, the author systematically reviews their own results and compares them with studies by various foreign authors, analyzing the similarities and differences in the data provided.

Dr. Nikolova presents 10 well-reasoned conclusions in her dissertation.

Contributions

The most significant contributions of the dissertation, with scientific and practical originality, can be summarized as follows:

- 1. An analysis was conducted on the subjective and objective signs of patients with persistent epithelial defects and their response to the assigned therapy, treated at the USBOBAL - Varna.*
- 2. An analysis was carried out on the etiology, subjective symptoms, and visual acuity, as well as a microstructural analysis of corneal changes through modern diagnostic methods before and after treatment.*
- 3. A map for evaluating the subjective and objective signs of patients with persistent epithelial defects was created.*
- 4. For the first time in Bulgaria, a detailed analysis and assessment of the etiology, diagnostic methods, and treatment of patients with persistent epithelial defects has been conducted.*
- 5. The advantages of biological therapy and an individualized approach to patients have been established as a more reliable method for treating patients with persistent epithelial defects compared to conventional moisturizing agents.*
- 6. In the surgical treatment of refractory cases, amniotic membrane transplantation is an economically advantageous and easily accessible option in modern ophthalmology for treating patients with persistent epithelial defects.*

Publications related to the dissertation topic

Dr. Nikolova has presented two publications related to the dissertation work. The abstract provides a concise yet comprehensive overview of the dissertation. Dr. Nikolova is a very precise and accurate young ophthalmologist. She is attentive to her patients and colleagues, goal-oriented, and focused on her career as an eye doctor.

Conclusion

The presented dissertation is a completed, well-structured, and thorough scientific work on the issues related to ocular surface pathology, particularly difficult and refractory conditions such as persistent epithelial defects (PED) and treatment options, specifically autologous serum eye drops. The dissertation meets all the requirements of the Law for the

Development of Academic Staff in the Republic of Bulgaria, the regulations for its application, and the relevant regulations of the Medical University of Varna.

Based on this, I have grounds to vote positively and propose to the Scientific Jury to vote positively for the award of the educational and scientific degree "Doctor" in the scientific specialty "Ophthalmology" to Dr. Neli Krūsteva Nikolova-Petkova.

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