SERUM DROPS—THE LAST RESORT FOR TOPICAL TREATMENT AFTER REFRACTIVE SURGERY AND LASER IN SITU KERATOMILEUSIS-INDUCED NEUROPATHIC EPITHELIOPATHY (LINE)

Nely Nikolova, Christina Grupcheva

Department of Ophthalmology and Visual Sciences, Faculty of Medicine, Medical University of Varna

ABSTRACT

INTRODUCTION: The idea to apply blood or blood product topical treatment is not new in ophthalmology, but about 40 years ago Ralph was the first to publish this idea. The biochemical properties of serum eye drops are very similar to the water component of the tears. Serum contains several growth factors, including epidermal growth factor, transforming growth factor-β and platelet-derived growth factors, nutrients and proteins, all of which are key components for tissue regeneration.

AIM: The aim of this article is to set a prospective study in order to identify and follow patients with laser in situ keratomileusis (LASIK)-induced neuropathic epitheliopathy (LINE) and analyze the benefits of the application of 20% autologous serum drops.

MATERIALS AND METHODS: A total of 16 subjects (10 females and 6 males) at a mean age of 34 years (19 the youngest and 41 the oldest) were recruited prospectively. All patients were seeking second opinion as they were bothered by discomfort, visual fluctuations, chronic red eye, and pain with different characteristics. Each patient was advised to have a week of wash-out period when only non-preserved artificial tears (Hyabak 0.15%, Thea ®) were applied. Then patients were advised to apply autologous serum drops four times (during the day), and assessment was done on 4th and 8th week. The primary outcome parameters were ocular surface disease index (OSDI), tear break-up time (TBUT) and corneal staining, the secondary included visual acuity and redness. Preparation of the autologous serum drops followed the in-house methodology.

RESULTS: The patients were significantly affected by their underdiagnosed condition. Statistical analysis of the outcome parameters demonstrated that only visual acuity did not change significantly. The main outcome parameter OSDI presented highest improvement from 57±12 to 12±6 after 8 weeks of application of 20% autologous serum drops. Corneal staining decreased and TBUT improved in all subjects.

CONCLUSION: Epithelial complications after LASIK are not uncommon and their recognition is the first step to long-term satisfaction of the patients with refractive procedures. After diagnosis of LINE after LASIK, especially with microkeratome, 20% autologous serum drops are an efficient long-term solution. The standard topical treatment usually takes 8 weeks to achieve good results.

Address for correspondence:
Nely Nikolova
Faculty of Medicine
Medical University of Varna
55 Marin Drinov St
9002 Varna
e-mail: nely_kr_nikolova@abv.bg

Keywords: *LASIK, epitheliopathy, autologous serum drops, ocular surface*

Received: May 15, 2022
Accepted: June 14, 2022

INTRODUCTION

The idea to apply blood or blood product topical treatment is not new in ophthalmology, but about 40 years ago Ralph was the first to publish this idea (1). The biochemical properties of serum eye drops are very similar to the water component of the tears (2). Serum contains several growth factors, including epidermal growth factor, transforming growth factor-β and platelet-derived growth factors, nutrients and proteins, all of which are key components for tissue regeneration.

Serum drops are often used by different protocols for dry eye treatment (3). More commonly they are used as treatment for chronic ocular surface problems caused by disease or infections (4–6). It is well known that different surgical procedures may also affect the ocular surface and exacerbate or initiate dry eye. One such procedure is the laser in situ keratomileusis (LASIK). Half of the patients would have dry eye after LASIK within the first week (2,7). This does not reduce dramatically in 4 weeks, where approximately 40% of the LASIK cases would experience dry eye. In half a year the percentage reduces to 20%, but usually these have long-term complaints and additional complications (8,9). Plasma-rich serum, umbilical cord products, and serum drops have been used for treatment of dry eye after LASIK with different success (4).

Although allogenic serum is a person's own product, it is relatively difficult to produce and prepare for prompt patient application. Having the expertise of the senior author for production of autologous serum in easy-to-use mono-doses, we set a prospective study to identify and follow patients with LASIK-induced neuropathic epitheliopathy (LINE).

MATERIALS AND METHODS

Patients were recruited prospectively. They had LASIK procedure in both eyes for moderate myopia, with a minimum period of 6 months prior to the study. Unfortunately, the information about surgical details like flap size, thickness, position and technology was not available for the purpose of the study. We recruited 16 subjects (10 females and 6 males) at a mean age of 34 years (the youngest was 19 and the oldest—41). According to the patients' notes the procedure went uneventful, and the vision restoration during the follow-up was more than 60% unaided. All patients were seeking second opinion as they were bothered by discomfort, visual fluctuations, chronic red eye, and pain with different characteristics. Each patient was using different drops, most commonly tear substitutes, but some patients were also using topical cyclosporine, dexamethasone, and even antibiotics. Not all of those drops were prescribed by the operating surgeon.

Upon inclusion of the study, ocular surface disease index OSDI (previously adopted to Bulgarian ophthalmic patients), full history, visual acuity, biomicroscopy (anterior and posterior segment), tear break-up time (TBUT), ocular surface staining (Efron scale), ocular redness (Efron scale) were established. Each patient was advised to have a week of wash-out period when only non-preserved artificial tears (Hyabak 0.15%, Thea ®) were applied. Then patients were advised to apply serum drops four times (during the day), and assessment was done on the 4th and 8th week. The primary outcome parameters were OSDI, TBUT and staining, the secondary visual acuity and redness.

Preparation and Handling of the Serum Drops

According to the experience of the senior author, 20% serum drops work best, so we used 6 vials (yellow top) to obtain serum from each patient. The serum was taken in aseptic conditions and diluted with NaCl 0.9% to 20% solution, which was placed in sterile, sealed, monodose plastic containers. The package with the monodose vials was flash frozen at -80°C and handed to the patient in a cooler. The patient was advised to freeze the package in a house freezer (usually -20°C) and defrost one container per day (which should be kept clean in the fridge area during the day). Some patients needed to bring a second container to work. Each patient was given instructions to apply drops 4x a day during wake up period.

RESULTS

The demographics of the 16 recruited subjects is presented on Table 1.

Most of the patients had more than one symptom at the time of inclusion in the study. Table 2 summarizes the complaints of all included patients.

Table 1. Demographics of the subjects diagnosed with LINE prior to inclusion in the study.

Parameter	Distribution
Gender	10 F; 6 M
Age	Mean of 34 y, range 19–41
Pre-operative refractive error	Myopia (2.0–7.5 D)
Laterality of complains	Two eyes: 13 subjects; one eye: only 3 subjects
Number of operations per eye	11: one operation; 5: one operation; one touch-up

Table 2. Summary of the complains of the subjects diagnosed with LINE prior to inclusion in the study.

Complaint	One Eye	Both Eyes
Discomfort	N/A	16
Visual fluctuations	2	14
Red eye	5	11
Mild pain	5	3
Moderate/severe pain	3	2

Dynamics of the primary outcome parameters before, 4 and 8 weeks after the treatment are presented in Table 3.

Table 3. Dynamics of the primary outcome parameters before, 4 and 8 weeks after the treatment with 20% autologous serum drops

Parameter	Baseline	4 Weeks After the Treatment with 20% Autologous Serum Drops	8 Weeks After the Treatment with 20% Autologous Serum Drops	Statistics (Baseline to Endpoint)
OSDI	57 ± 12	26 ± 8	12 ± 6	P = 0.001
TBUT	7 ± 3	10 ± 5	12 ± 3	P = 0.02
Staining	3.7	2.9	1.4	P = 0.009

Dynamics of the secondary outcome parameters before, 4 and 8 weeks after the treatment are presented in Table 4.

The statistical analysis of the outcome parameters showed that only visual acuity did not change significantly. The main outcome parameter OSDI demonstrated highest improvement. Analysis among patients with one or both eyes presenting with LINE, did not show any specific correlations. Interestingly, the greatest improvement based on OSDI was encountered in patients who suffered from moderate to severe pain in both eyes.

DISCUSSION

LASIK is the most commonly performed refractive procedure in the world, and definitely the most common (more than 70%) refractive surgical procedure in Bulgaria (10,11). Regardless of the equipment used for flap formation (microkeratome or femtosecond laser), the corneal nerves are cut and severely damaged (11,12). This reduces the basic and reflex tear formation, affects the blinking mechanism and also may lead to neurotrophic complications. More than 20% of the patients experienced discomfort from dry eye during the first year (2). Some of the patients really suffered from this condition (13). Unfortunately, in our study we had no information about

Table 4. Dynamics of the secondary outcome parameters before, 4 and 8 weeks after the treatment with 20% autologous serum drops

Parameter	Baseline	4 Weeks After the Treatment with 20% Autologous Serum Drops	8 Weeks After the Treatment with 20% Autologous Serum Drops	Statistics (Baseline to Endpoint)
Visual acuity	0.56	0.66	0.67	P = 0.06
Redness	2.7	1.9	0.9	P = 0.03

the surgical procedures, as the patients requested confidential consultation and requested their history to be kept from the surgical center.

In the published literature LINE is more often associated with mechanical microkeratome than with femtosecond created flap (14). In Bulgaria femtosecond is rarely used and therefore we should expect more patients with LINE. Our small study provides solid evidence that those patients will benefit from autologous serum drops. Moreover, this will not only help the patient, but also will support the surgeon in the process of faster treatment of this not uncommon complication.

There are variety of methodologies to produce autologous serum drops. In the literature the most popular concentrations are 100%, 50%, and 20% (4,15). The latter is based on the rationale that TGF beta is 5 times more concentrated in the serum than in the tears. In this study and also in some prior studies, we demonstrated the efficiency of this concentration (4,15). Moreover, none of our patients reported any problems with the drops. This is important because we use unique package such as small daily containers, which might also induce difficulties when the patient applies their drops.

Autologous serum drops are proven therapy for moderate to severe dry eye. In many countries they are unlicensed medication and they are subject of special regulations (16, 17). Most of the learned ophthalmology societies in Europe are having special guidelines for preparation and application of such products (18). Currently, this therapy is not recommended for young children. Indications are also quite broad and in the literature there are occasional reports of a number of rare diseases. This however provides an opportunity and eye care practitioners with therapeutic license must consider this option for ocular surface restoration.

CONCLUSION

Epithelial complications after LASIK are not uncommon and their recognition is the first step to long-term satisfaction of the patients with refractive procedures. LINE is one of those complications, which even when properly recognized is often a therapeutic challenge. After diagnosis of LINE after LASIK, especially with mechanical microkeratome, 20% autologous serum drops are an efficient long-term solution. The standard treatment usually takes 8 weeks to achieve good results, but longer treatment might also be considered.

REFERENCES

1. Higuchi A. Autologous serum and serum components. Invest Ophthalmol Vis Sci. 2018;59(14):DES121-9. doi: 10.1167/iovs.17-23760.
2. Toda I. Dry eye after LASIK. Invest Ophthalmol Vis Sci. 2018;59(14):DES109-15. doi: 10.1167/iovs.17-23538.
3. Cui D, Li G, Akpek EK. Autologous serum eye drops for ocular surface disorders. Curr Opin Allergy Clin Immunol. 2021;21(5):493-9. doi: 10.1097/ACI.0000000000000770.
4. Rodríguez Calvo-de-Mora M, Domínguez-Ruiz C, Barrero-Sojo F, Rodríguez-Moreno G, Antúnez Rodríguez C, Ponce Verdugo L, et al. Autologous versus allogeneic versus umbilical cord sera for the treatment of severe dry eye disease: a double-blind randomized clinical trial. Acta Ophthalmol. 2022;100(2):e396-e408. doi: 10.1111/aos.14953.
5. van der Meer PF, Verbakel SK, Honohan Á, Lorinser J, Thurlings RM, Jacobs JFM, et al. Allogeneic and autologous serum eye drops: a pilot double-blind randomized crossover trial. Acta Ophthalmol. 2021;99(8):837-42. doi: 10.1111/aos.14788.
6. Valencia Castillo SL, Martín ES, García Frade LJ, García-Miguel FJ. Autologous serum eye drops improve tear production, both lachrymal flow and stability tests and conjunctival impression cytology with transfer in dry eye disease. Blood Transfus. 2021;19(1):45-53. doi: 10.2450/2020.0009-20.
7. Moshirfar M, Masud M, Shah TJ, Avila MR, Hoopes PC Sr. Chemical conjunctivitis and diffuse lamellar keratitis after removal of eyelash extensions. Am J Ophthalmol Case Rep. 2018;12:21-3. doi: 10.1016/j.ajoc.2018.07.007.
8. Wang L, Cao K, Wei Z, Baudouin C, Labbé A, Liang Q. Autologous serum eye drops versus artificial tear drops for dry eye disease: a systematic review and meta-analysis of randomized controlled trials. Ophthalmic Res. 2020;63(5):443-51. doi: 10.1159/000505630.
9. Marchand M, Harissi-Dagher M, Germain M, Thompson P, Robert MC. Serum drops for ocular surface disease: national survey of Canadian cornea specialists. Can J Ophthalmol. 2018;53(3):266-71. doi: 10.1016/j.jcjo.2017.09.007.

10. Wu Y, Xu L, Song Y, Zhang Q, Qin G, Yang L, et al. Management of post-LASIK dry eye with intense pulsed light in combination with 0.1% sodium hyaluronate and heated eye mask. Ophthalmol Ther. 2022;11(1):161-76. doi: 10.1007/s40123-021-00418-2.

11. Abdel-Radi M, Abdelmotaal H, Anwar M. Thin-flap laser in situ keratomileusis-associated dry eye: a comparative study between femtosecond laser and mechanical microkeratome-assisted laser in situ keratomileusis. Eye Contact Lens. 2022;48(1):20-6. doi: 10.1097/ICL.0000000000000850.

12. Chao C, Zhou S, Stapleton F, Chen S, Zhou X, Golebiowski B. The structural and functional corneal reinnervation mechanism at different regions after LASIK-an in vivo confocal microscopy study. Graefes Arch Clin Exp Ophthalmol. 2022;260(1):163-72. doi: 10.1007/s00417-021-05381-z.

13. Moshirfar M, Bhavsar UM, Durnford KM, McCabe SE, Ronquillo YC, Lewis AL, et al. Neuropathic Corneal Pain Following LASIK Surgery: A Retrospective Case Series. Ophthalmol Ther. 2021;10(3):677-89. doi: 10.1007/s40123-021-00358-x.

14. Salomão MQ, Ambrósio R Jr, Wilson SE. Dry eye associated with laser in situ keratomileusis: Mechanical microkeratome versus femtosecond laser. J Cataract Refract Surg. 2009;35(10):1756-60. doi: 10.1016/j.jcrs.2009.05.032.

15. López-García JS, García-Lozano I, Rivas L, Viso-Garrote M, Raposo R, Méndez MT. Lyophilized autologous serum eyedrops: experimental and comparative study. Am J Ophthalmol. 2020;213:260-6. doi: 10.1016/j.ajo.2020.01.027.

16. Shtein RM, Shen JF, Kuo AN, Hammersmith KM, Li JY, Weikert MP. Autologous serum-based eye drops for treatment of ocular surface disease: a report by the American Academy of Ophthalmology. Ophthalmology. 2020;127(1):128-33. doi: 10.1016/j.ophtha.2019.08.018.

17. Hirayama M. Advances in functional restoration of the lacrimal glands. Invest Ophthalmol Vis Sci. 2018;59(14):DES174-82. doi: 10.1167/iovs.17-23528.

18. Lagnado R, King AJ, Donald F, Dua HS. A protocol for low contamination risk of autologous serum drops in the management of ocular surface disorders. Br J Ophthalmol. 2004;88(4):464-5. doi: 10.1136/bjo.2003.025528.