

(33)

Treatment of post-burn persistent corneal ulcers with excimer laser phototherapeutic keratectomy. Prospective clinical trial

Fototerapeutyczna keratektomia laserowa w leczeniu uporczywego owrzodzenia rogówki powstałego po jej oparzeniu. Badania kliniczne

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Summary:

Purpose: To evaluate efficacy of excimer laser phototherapeutic keratectomy (PTK) in treatment of patients with post-burn persistent corneal ulcers.

Material and methods: Study design – nonrandomized trial with a "historic" control group. 54 eyes (53 patient) with central superficial post-burn corneal ulcers that were formed in different time frame (18-104 days) after grade IV burns were included into the study. Among these 26 patients (26 eyes) were included prospectively – they underwent 1-time PTK. Control group consists of 27 patients (28 eyes), who underwent surgical keratectomy of ulcer edge and base. Indication for surgery in both groups was non-decreasing size of ulcer during 7-14 days of conventional treatment. Patients of both groups wore therapeutic contact lenses after surgery. Outcome measures were number of cases of corneal healing, number of complications, terms of corneal epithelialization, visual acuity.

Results: PTK promoted corneal healing in 24/26 patients, surgical keratectomy was effective in 27/28 patients. PTK 1) did not lead to complications (one corneal perforation in control group), 2) accelerated corneal epithelialization on 18,4 days compared to surgical keratectomy group ($p = 0.000$, Kruskal-Wallis test), 3) improved mean visual acuity on 0.08 compared to control group in 6 months follow-up examination (Bonferroni corrected $p = 0.002$, Kruskal-Wallis test).

Conclusion: PTK is a safe and effective method for treatment of post-burn superficial persistent corneal ulcers recalcitrant to conventional therapy.

Słowa kluczowe: wrzód rogówki, oparzenie oka, laser ekscymerowy, fototerapeutyczna keratektomia.
Key words: corneal ulcer, eye burn, excimer laser, phototherapeutic keratectomy.

Introduction

Formation of persistent corneal ulcers is a frequent complication of severe eye burns – grade IV (1). Corneal ulceration process may lead to perforation in some cases. Conventional therapy of such ulcers usually consists of lubricants – promoters of epithelialization, collagenase inhibitors and bandage contact lenses. However, main disadvantage of lubricants is long duration of treatment; application of collagenase inhibitors has shown unsatisfactory results in treatment of post-burn corneal ulceration (2); contact lens wear (3) needs further trials due to lack of patients with persistent ulcers of burn etiology. Surgical methods such as lamellar corneal grafting (4), conjunctival flap (5), amniotic membrane transplantation (6) promote corneal healing in most cases, but the process

often results in dense corneal opacity formation and low visual acuity. That is why search for adequate surgical tool for treatment of persistent post-burn corneal ulcers seems to be necessary.

Excimer laser phototherapeutic keratectomy (PTK) with wavelength of 193 nm has been applied in treatment of a number of corneal pathologies during past decades (7). Kottek A, et al. (8) successfully applied excimer laser PTK in the treatment of persistent erosion of corneal graft in a patient with ocular burn but further studies of the PTK application in treatment of post-burn corneal erosions and ulcers have not been conducted. In this study we compare PTK with conventional treatment of persistent corneal ulcers of burn etiology in our patients.

Groups of patients/ Grupy pacjentów	Number of patients/ Liczba pacjentów	Sex/ Płeć		Age/ Wiek M ± SD	Etiologia oparzenia (liczba oczu)			Duration of ulcer (days after burn) M ± SD/ Czas trwania wrzodu (dni po oparzeniu) M ± SD	Visual acuity M ± SD/ Ostrość wzroku M ± SD
		m	f		therm	alkali	acid		
PTK	26	20	6	44.2 ± 15.5	6	20	-	51.3 ± 25.5	0.03 ± 0.05
Surgical keratectomy/ Chirurgiczna keratektomia	27	23	4	38.7 ± 13.1	3	20	5	41.7 ± 18.2	0.04 ± 0.12
P		0.501		0.139	0.293	0.750	0.051	0.275	0.101

Tab. 1. Demographics and clinical data at the beginning of the study.
Tab. 1. Demograficzne i kliniczne dane z początku obserwacji.

Material and methods

The study was carried out with approval of the Bioethics Committee of the Filatov Institute of Diseases and Tissue Therapy. Written informed consent was obtained from all patients.

53 patients – 54 eyes with post-burn superficial corneal ulcers which were formed in different time frame (18-104 days, mean 54.3, SD 27.8) after grade IV burns (1) were included into the study. All patients with post-burn superficial persistent ulcers treated at the Department of Eye Burns between January 2003 and December 2007 consecutively underwent 1-time PTK (26 patients – 26 eyes). 27 patients (28 eyes) who were treated at the Department between January 2000 and December 2003 were included in the control group. The patients from the control group underwent superficial surgical keratectomy of ulcer edges and base in case of corneal ulcer persistence. There were no inside group differences in sex, age, burn etiology, visual acuity and terms of corneal ulcer persistence at the beginning of the study (Tab. 1).

Exclusion criteria

Deep post-burn corneal ulcer, superficial corneal ulcer connected to the limbus and paralimbal conjunctival ischemia or necrosis.

Indication for surgery

Non-decreasing size of superficial ulcer during 7-14 days of conventional treatment (lubricants – dexapanthenol 0.5% 6 times daily, ascorbic acid 5% 1 ml daily in subconjunctival injections).

Phototherapeutic Keratectomy

We used "Schwind Keratom" (Schwind, Kleinostheim, Germany) excimer laser machine. Topical proparacaine 0.5% was used preoperatively. Multifocal PTK 1 mm in diameter and 3-8 μ m depth has been applied to ablate epithelium at ulcer edge. Ablation of stroma has been performed after ablation of epithelium. Diameter of ablation of stroma was equal to the maximal size of ulcer. Modes of excimer laser machine at ablation of 20-38 μ m of corneal tissue have been used. Criterion of PTK sufficiency was removal of whitish debris from ulcer edges and base.

Surgical Keratectomy

Scraping with scalpel was performed under operating microscope after topical proparacaine 0.5% anesthesia in control group to remove debris from corneal ulcer edges and base. Criterion of surgical keratectomy sufficiency was the same as in PTK group.

Post-operative care

Patients of both groups wore bandage soft contact lens until corneal epithelialization. Drops of antiseptic (octenisept, dioxidine), non-steroidal anti-inflammatory agents (diclofenac 0.1%) were applied 2-3 times daily until corneal healing. The patients were seen daily until corneal epithelialization was finished, and in 3 and 6 months thereafter.

Clinical efficacy criteria

It were absence of complications (deepening of the ulcer, corneal perforation), time of corneal healing (days after the surgery), presence of corneal defect recurrences, visual acuity after corneal healing and in 6 months thereafter. Cornea was considered epithelialized when it was not stained after 1 drop of fluoresceinum 0.1% instillation. Visual acuity was measured with Golovin-Sivtsev chart – Cyrillic analogue of Snellen chart. Visual acuity data was expressed in decimal numbers and it was not converted into logMAR data because visual acuity was less than 0.1 in majority of patients. The visual acuity of patients who could not distinguish visual-acuity chart at a distance of 1 m was assessed by asking whether they could count fingers presented by the examiner. If not, visual acuity was recorded as the ability to see hand movement of the examiner.

Statistics

Mean (M), standard deviation (SD), 90% and 95% confidence intervals were assessed for quantitative variables. For purposes of statistical analysis counting fingers was categorized as visual acuity of 0.005, hand motion as 0.002. Non-parametric Kruskal-Wallis test was applied to evaluate intergroup differences. Bonferroni correction factor was used in case of plural comparisons in follow-up analysis. Two-tailed Fisher exact test was used to evaluate intergroup differences in sex, burn etiology, cases of corneal healing, number of complications, number of recurrences.

Efficacy criteria/ Kryteria skuteczności	Corneal healing achievement (cases)/ Osiągnięte zagojenie rogówki (przypadki)		Recurrences of corneal ulcers (cases)/ Nawroty wrzodu rogówki (przypadki)		Terms of corneal epithelialization (days) M ± SD/ Czas epitelializacji rogówki (dni) M ± SD	
	PTK	Surgical keratectomy	PTK	Surgical keratectomy	PTK	Surgical keratectomy
Groups of patients/ Grupy pacjentów	24/26 92.3%	27/28 96.4%	4/24 16.7%	2/27 7.4%	12.0 ± 7.6	30.4 ± 12.1
95% C*					8.8-15.2	25.6-35.2
P	0.603		0.412		0.000	

Tab. II. Results of PTK and surgical keratectomy application.

Tab. II. Wyniki PTK i chirurgicznej keratektomii.

* CI – confidence interval

Results

Summarized results of PTK and surgical keratectomy application are presented in Table II. PTK promoted corneal healing in 24 of 26 patients (92.3%). Surgical procedure was well tolerated by all patients. PTK with estimated parameters did not lead to deepening of existing corneal ulcers, no perforations were observed. The ulcer size increased at the first day postop., epithelialization started at the 2nd-4th day and finished in 5-30 days after operation (Mean 12.0, SD 7.6). Recurrences of corneal defects occurred in 4 of 24 successful cases in 5-10 days after epithelialization of the cornea (Tab. II). Spontaneous healing in these cases occurred in 28-36 days after PTK. In long term follow-up (3 and 6 months) no recurrences occurred.

In 2 cases, when PTK was ineffective (persistent and the same size of ulcer during 2 weeks after the operation), corneal healing occurred after amniotic membrane transplantation (1 case) and after lamellar corneal grafting (1 case).

In control group corneal healing occurred in 27 of 28 eyes (96.4%). Epithelialization started in 5-7 days and finished in 12--49 days after surgical keratectomy (Mean 30.4, SD 12.1) – Table II. In one case corneal perforation occurred due to long persisting ulcer 6 months after surgical keratectomy. This patient underwent lamellar corneal grafting. Recurrences of corneal defects in control group occurred in 2 among 27 successful cases in 3 and 7 days after corneal healing. Re-epithelialization was achieved after conjunctival flap in both cases.

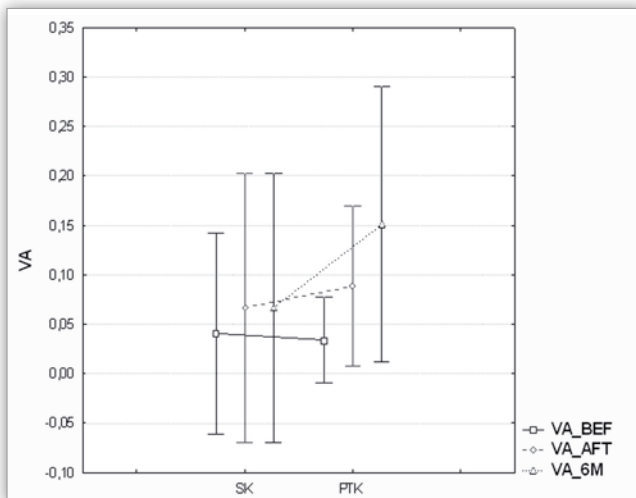


Fig. 1. Visual acuity dynamics in patients of PTK and surgical keratectomy groups.

Footnotes: VA – visual acuity, SK – surgical keratectomy group, PTK – phototherapeutic keratectomy group, VA_BEF – visual acuity (M ± SD) before the surgery, VA_AFT – visual acuity (M ± SD) after cornea was healed, VA_6M – visual acuity (M ± SD) 6 months after the surgery.

Ryc. 1. Dynamika ostrości wzroku u pacjentów z grupy PTK i z grupy po chirurgicznej keratektomii.

Oдноśnik: VA – ostrość wzroku, SK – grupa po chirurgicznej keratektomii, PTK – grupa po keratektomii fototerapeutycznej, VA_BEF – ostrość wzroku (M ± SD) przed operacją, VA_AFT – ostrość wzroku (M ± SD) po zagojeniu rogówki, VA_6M – ostrość wzroku (M ± SD) 6 miesięcy po operacji.

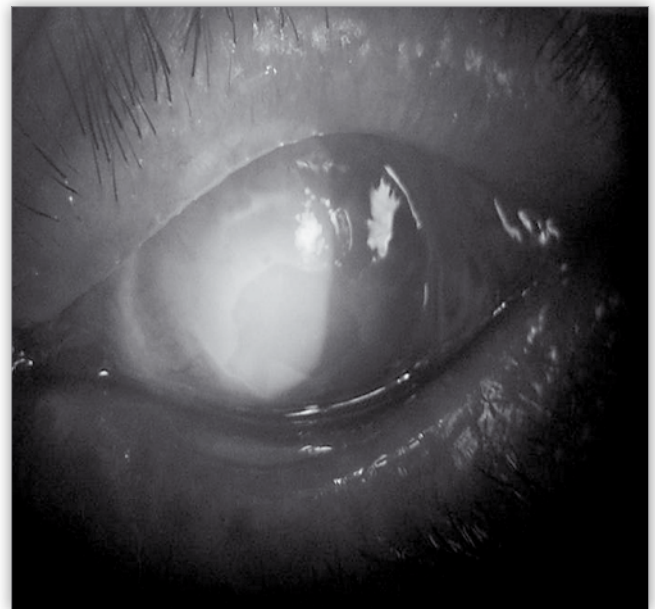


Fig. 2a. A patient from PTK group. The 36th day after grade IV thermal burn. Dense corneal opacity, superficial ulcer of irregular form in the optical zone, superficial vessels in the cornea. Visual acuity 0.04.

Ryc. 2a. Pacjent z grupy PTK. 36 dni po oparzeniu termicznym IV stopnia. Znaczne przymglenie rogówki, powierzchowne owrzodzenie o nieregularnym kształcie w strefie optycznej, powierzchowne naczynia w rogówce. Ostrość wzroku 0,04.

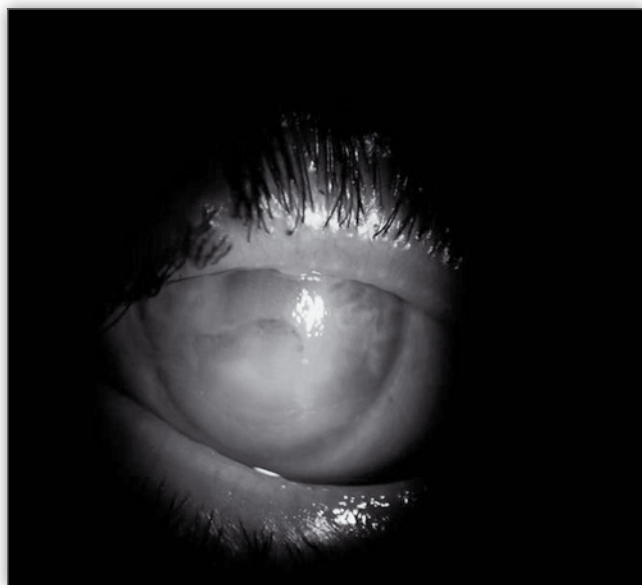


Fig. 2b. A patient from surgical keratectomy group. The 34th day after grade IV thermal burn. Dense corneal opacity, superficial ulcer in the optical zone 7 x 6 mm. Visual acuity 0.04.

Ryc. 2b. Pacjent z grupy chirurgicznej keratektomii. 34 dni po oparzeniu termicznym IV stopnia. Znaczne przymglenie rogówki, powierzchowne owrzodzenie w strefie optycznej 7 mm x 6 mm. Ostrość wzroku 0,04.

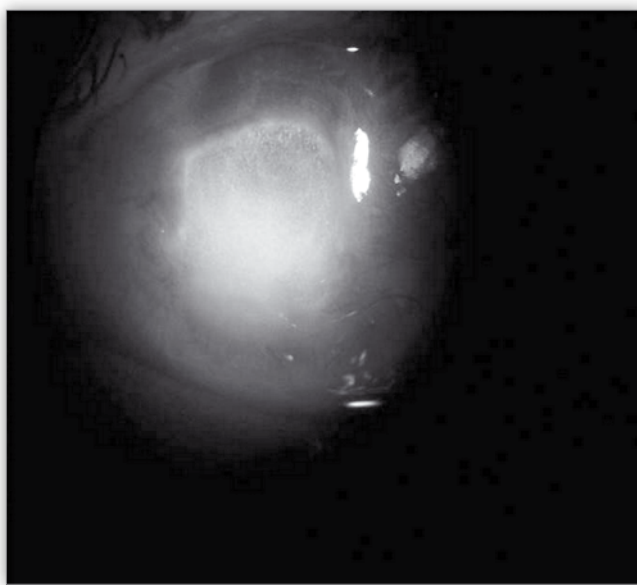


Fig. 2d. The same patient as in Fig. 2b. The 24th day after surgical keratectomy (the 59th day after the burn). Corneal ulcer of the same size with infiltrated edges and base. Visual acuity 0.04.

Ryc. 2d. Ten sam pacjent (jak na ryc. 2b) 24 dni po chirurgicznej keratektomii (59 dni po oparzeniu). Wrzód rogówki o tych samych wymiarach z nacieczonymi brzegami i podstawą. Ostrość wzroku 0,04.

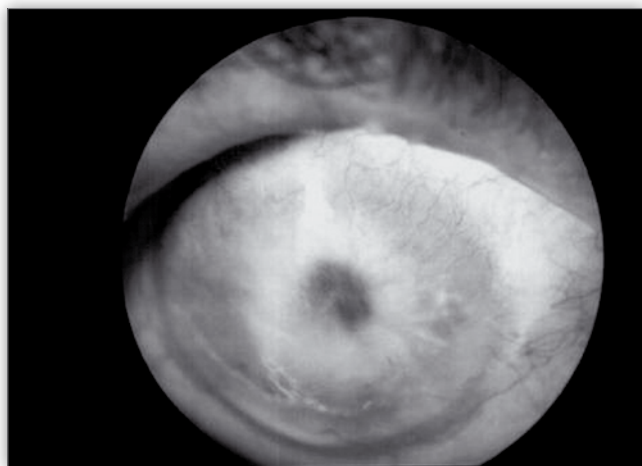


Fig. 2c. The same patient as in Fig. 2a. The 12th day after PTK (the 49th day after the burn). Smooth epithelial surface, decrease of corneal opacity density. Visual acuity 0.08.

Ryc. 2c. Ten sam pacjent (jak na ryc. 2a) 12 dni po PTK (49. dzień po oparzeniu). Gładka powierzchnia nabłonka, zmniejszenie przymglenia rogówki. Ostrość wzroku 0,08.

95% confidence interval for intergroup difference in terms of corneal healing ($30.4-12.0 = 18.4$ days) was 12.8-24.0 days.

Increase of corneal clarity, which has been noticed in follow-up period after PTK, led to visual acuity improvement. Mean visual acuity after corneal healing in PTK group was 0.09 ± 0.08 , in 6 months follow-up $- 0.15 \pm 0.14$. In patients from surgical keratectomy group mean visual acuity in follow-up period did not change. Immediately after corneal healing and in 6 months after it was 0.07 ± 0.15 (intergroup Bonferroni corrected P after corneal healing = 0.009, in 6 months = 0.002)

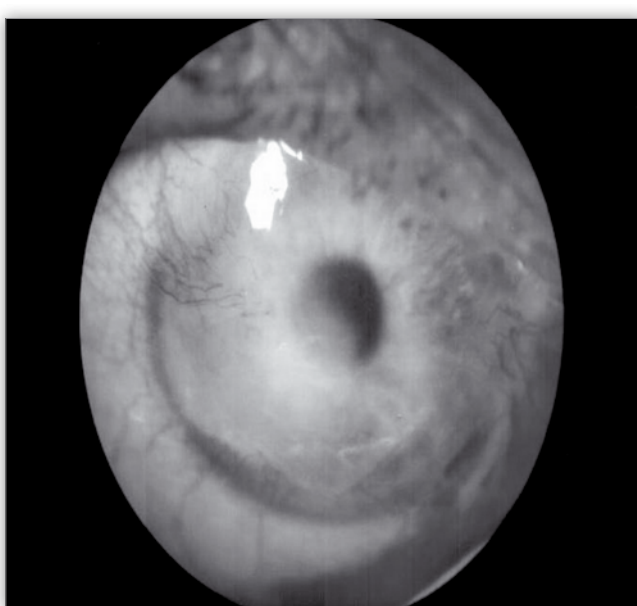


Fig. 2e. The same patient as in Fig. 2a, 2c. 6 months after PTK. Smooth, stable epithelial surface, non-dense corneal opacity, single corneal vessels. Visual acuity 0.12.

Ryc. 2e. Ten sam pacjent (jak na ryc. 2a, 2c) – 6 miesięcy po PTK. Gładka, stabilna powierzchnia, przymglenie rogówki mniejsze, pojedyncze naczynia w rogówce. Ostrość wzroku 0,12.

– Fig. 1. 90% confidence interval for intergroup difference in mean visual acuity in 6 months follow-up ($0.15-0.07 = 0.08$) was 0.01-0.15.

Clinical examples of PTK and surgical keratectomy effect at the healing of post-burn corneal ulcers are presented in Fig. 2a-f.

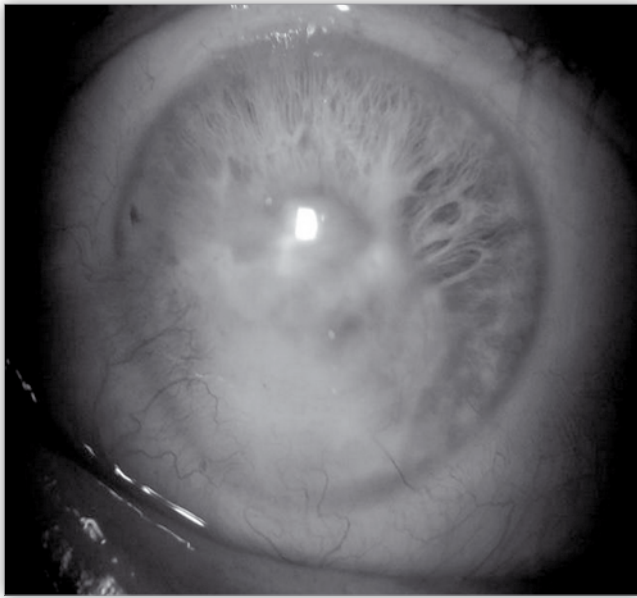


Fig. 2f. The same patient as in Fig. 2b, 2d. 6 months after surgical keratectomy. Dense corneal opacity. Visual acuity 0.04.

Ryc. 2f. Ten sam pacjent (jak na ryc. 2b, 2d) – 6 miesięcy po chirurgicznej keratektomii. Znaczne zmętnienie rogówki. Ostrość wzroku 0,04.

Discussion

This was a pilot study where excimer laser PTK efficacy in treatment of post-burn persistent corneal ulcers was evaluated. In our opinion, surgical keratectomy was an ideal procedure to use as a “positive control” to evaluate PTK efficacy because of its similar influence on corneal tissue compare with excimer laser keratectomy (9,10). Besides, efficacy of surgical keratectomy as a treatment method of persistent post-burn corneal erosions and ulcers, in spite of years of application, was never reported previously.

Our data suggests that PTK is a safe and effective treatment for superficial persistent corneal ulcers of burn etiology, which confirm results of experimental studies (11), where acceleration of corneal healing after PTK was shown. It seems to be a good alternative therapy to surgical keratectomy despite of high cost due to considerable shortening of treatment duration, faster release from signs of tearing, photophobia and improvement of visual outcome in these patients. Another advantage of PTK it is precisely controlled removal of stroma better than done manually. However, parallel retrospective analysis of surgical keratectomy efficacy that was conducted in this study showed that this procedure is still applicable in treatment of persistent post-burn corneal ulcers due to its simplicity and safety, although difference in efficacy between surgical keratectomy and conventional therapy of these patients with lubricants and bandage contact lenses remains unclear.

3 of 4 recurrences in PTK group were caused by mixed infection (bacterial or viral conjunctivitis) in long term follow-up after the procedure. That is why we consider that PTK itself was not a reason of corneal surface instability in these cases. Reasons of recurrences in control group from case histories could not be elucidated.

Another excimer laser PTK drawback is refractive shift (12,13). We could not evaluate presence or absence of refrac-

tive shift in the successful patients because it was impossible to evaluate refractive error due to dense central corneal opacities. We assume that central PTK treatment caused hyperopia and perhaps astigmatism in our cases, but no correction (neither glasses nor contact lenses) could be applied. Similarly, we could not assess presence of “haze” due to dense corneal opacity formation, but increase of leucoma density after PTK (an indirect sign of “haze” in our cases) was not observed in any patient.

Results of excimer laser PTK treatment appears to be promising, but the 6 months follow-up period is relatively short. A longer postoperative follow-up time is necessary for a more reliable assessment of clinical stability. Another relative disadvantage of this study it is retrospective character of control group. Of course, prospective randomized trial would give more exact results of PTK efficacy, but it will be a difficult task due to little number of these patients.

On our opinion, PTK could also be used as a preparatory procedure for subsequent conventional surgery (amniotic membrane transplantation, conjunctival flap or lamellar corneal graft) in case of already existing deep corneal ulceration due to its ability of very precise removal of debris from ulcer base and edges with simultaneous promotional effect at corneal regeneration. Positive effect at corneal regeneration of combination of excimer laser keratectomy and amniotic membrane transplantation was reported previously (14,15).

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2. Kurs „ELEKTROFIZJOLOGIA NARZĄDU WZROKU” Poznań, 26-27 listopada 2010



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PROGRAM KURSU:

piątek 26.11.2010 – godzina 11.00

1. Dr med. Izabela Kulińska-Niedziela • Anatomia i fizjologia siatkówki oraz drogi wzrokowej w aspekcie badań elektrofizjologicznych
2. Dr hab. n. med. Maciej Krawczyński • Schorzenia genetycznie uwarunkowane narządu wzroku i ich diagnostyka
3. Dr Mikołaj Meller • Schorzenia nabyte narządu wzroku i ich diagnostyka
4. Dr med. Jadwiga Bernardczyk-Meller • Wprowadzenie do badań elektrofizjologicznych i psychofizycznych
5. Dr Marta Pawlak • Standardy ISCEV badań elektrofizjologicznych
6. Dr med. Jadwiga Bernardczyk-Meller • Elektroretinografia w schorzeniach narządu wzroku
7. Dr hab. n. med. Wojciech Lubiński • mfERG
8. Dr hab. n. med. Wojciech Lubiński • Badania elektrofizjologiczne w jaskrze

sobota 27.11.2010 godzina 8.00

1. Dr med. Jadwiga Bernardczyk-Meller • Inne badania elektrofizjologiczne narządu wzroku (PERG, EOG, focal ERG)
2. Dr med. Dorota Pojda-Wilczek • Wzrokowe potencjały wywołane – wskazania i podstawy interpretacji
3. Dr med. Dorota Pojda-Wilczek • Wykorzystanie badań elektrofizjologicznych w praktyce okulistycznej
4. Dr med. Jadwiga Bernardczyk-Meller • Badania elektrofizjologiczne dzieci i niemowląt
5. Dr hab. n. med. Sławomir Michalak • Znaczenie badań elektrofizjologicznych narządu wzroku w neurologii ze szczególnym uwzględnieniem zespołów paranowotworowych
6. Dr med. Jadwiga Bernardczyk-Meller • Podsumowanie kursu, prezentacja ciekawych przypadków