RESEARCH ARTICLE

Micropulse Cyclophotocoagulation vs Selective Laser Trabeculoplasty: Effects on Corneal Endothelial Cells and Intraocular Pressure

Aylin Garip Kuebler[1], Siegfried Priglinger[2], Lukas Reznicek[3]

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Abstract

Purpose: To evaluate the effects of micropulse transscleral cyclophotocoagulation (mCPC) and selective laser trabeculoplasty (SLT) on endothelial cell density (ECD) and reduction of the intraocular pressure (IOP) in patients with primary-open angle glaucoma (POAG).

Patients and Methods: In this observational, retrospective study, 40 eyes with POAG were included. Patients were divided into three groups—group I was treated with SLT (n = 13), group II was treated with mCPC (n = 13), and group III included age-matched patients with medically treated glaucoma (n = 14) (control group). In both treatment groups (SLT and mCPC) preoperative and postoperative findings of best-corrected visual acuity (BCVA), ECD, and IOP were compared to the control group.

Results: The mean time interval before and after the treatment was 215 ± 120 days in group I (SLT) and 273 ± 177 days in group II (mCPC). The follow-up for group III (control group) was 209 ± 103 days. In both treatment groups (SLT and mCPC) there was a statistically significant reduction of the IOP postoperatively (group I: 3.5 ± 3.7 mm Hg (p = 0.005) and group II: 4.3 ± 4.1 mm Hg (p = 0.003)). The mean IOP for group III was 12.9 ± 3.7 mm Hg at visit 1 and did not change significantly (p = 0.353) at visit 2. In all three groups, there was no statistically significant change in ECD at the last visit.

Conclusion: According to our results, both SLT and mCPC seem to be effective in lowering the IOP, without showing any statistically significant effect on ECD in patients with POAG.

However, larger and longer-term studies are necessary to understand the effects of the SLT and mCPC procedures on ECD.

Keywords: Corneal endothelial cell density, Intraocular pressure, Micropulse cyclophotocoagulation, Selective laser trabeculoplasty.

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Introduction

Glaucoma is a slow-progressing disease that causes degeneration of retinal ganglion cells, loss of retinal nerve fiber layers, and degeneration of the optic nerve head. Patients suffering from glaucoma present with visual field defects and a decrease in visual acuity as well as contrast sensitivity. The disease remains the leading cause of irreversible blindness worldwide.[1] Its well-known risk factors include high IOP, old age, use of corticosteroids (systematic/local), African-Caribbean ethnicity, family history of glaucoma, and central corneal thickness.[2] Lowering the IOP is shown to be the most effective treatment in slowing down, and even stopping the progression of the disease.[3]

Micropulse transscleral cyclophotocoagulation (mCPC) has recently been presented as a promising technique in glaucoma treatment. mCPC is designed to apply repetitive micropulses of diode laser energy which is absorbed by targeted pigmented tissues causing coagulative necrosis. Due to the "on and off" design of the method, non-pigmented tissues (which cool down during the "off" mode) are protected from potential collateral damage.[4] In contrast to the established cyclophotocoagulation (CPC), mCPC uses significantly less energy and is clinically better tolerated by the treated patients.[4] Interestingly, according to some authors, mCPC should be considered as an early treatment for the management of glaucoma alternative to incisional glaucoma surgeries in patients with relatively good BCVA (BCVA ≥ 20/60 was considered as a good BCVA in the research).[5]

[1–3]Department of Ophthalmology, Ludwig-Maximilians-University, Munich, Germany

Corresponding Author: Aylin Garip Kuebler, Department of Ophthalmology, Ludwig-Maximilians-University, Munich, Germany, Phone: +4989440053812, e-mail: aylin.garip-kuebler@med.uni-muenchen.de; aylingarip@gmail.com

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Selective laser trabeculoplasty (SLT) is a well-known technique in glaucoma treatment. SLT was first developed in dermatology in the 1980s. In 1995, Latina et al. proposed using SLT with a green (532 nm), Q-switched, frequency-doubled neodymium-doped yttrium aluminum garnet (Nd:YAG) laser in ophthalmology.[6,7] In 2001, the Food and Drug Administration approved SLT, and since then, numerous clinical articles have evaluated the efficiency and safety of the method. Recent work has noted dark spots and corneal abnormalities as transient effects of the SLT procedure.[8]

The corneal endothelium, a single layer of hexagonal-shaped cells, is critical to a healthy cornea, enabling clear vision. From age 15–85, physiologically normal corneas lose about 0.6% of their ECD every

year.[9,10] Higher ECD loss is reported after glaucoma surgeries such as Ahmed glaucoma valve (AGV) implants and Baervaldt implants as well as after trabeculectomy. We still do not know, however, how critical treatments, such as mCPC and SLT affect ECD in glaucoma patients. In one study, the authors reported the effects of Cyclodiode photocoagulation (CPC) on clear corneal grafts developing corneal opacification and edema after the CPC treatment.[11]

Our research evaluated both methods, mCPC, and SLT, in terms of their capacity to lower IOP as well as their potential for ECD relative to a control group of medically treated glaucoma patients.

Patients and Methods

This is an observational and retrospective cross-sectional study including 40 patients. Our study adhered to the tenets of the Declaration of Helsinki.

Participants

The study sample comprised 40 patients with POAG treated at the Glaucoma Practice Prof. Lachenmayr and PD Dr. Reznicek, Munich, Bavaria,Germany between 2018 and 2020. We included all patients who underwent mCPC and SLT with an existing preoperative and postoperative ECD. Our aim was to assess mCPC and SLT methods in terms of the reduction of IOP and ECD loss relative to a control group of patients receiving medical treatment only.

Data were compiled and analyzed using Statistical Package for the Social Sciences (SPSS) Version 26.0 (SPSS Inc, Chicago, IL, USA). None of the originally included patients had to be excluded during the process of further evaluation. Inclusion criteria manifests POAG with uncontrolled IOP in spite of having the maximum tolerated medical treatment.

Exclusion criteria were previous glaucoma surgery, previous intraocular surgery except for cataract surgery >6 months, participant age being <20 years, corneal diseases, and presence of an anterior chamber intraocular lens.

The patients were divided into three groups by therapy method. Group I (n = 13) underwent SLT, group II (n = 13) underwent mCPC, and group III (n = 14) received antiglaucomatous medication only. The control group was age-matched to mCPC and SLT patients.

In all patients, a complete ophthalmic examination was performed—BCVA was assessed with decimal charts, slit-lamp biomicroscopy, and measurement of the IOP with Goldmann tonometry. All examinations were performed by a single ophthalmologist (LR). Baseline data including age at the time of the treatment, sex, type of glaucoma, glaucoma medications (for the control group), lens status, and cup-disc-ratio were documented.

The following parameters, measured before and after treatment, were used in the statistical analysis—BCVA tested with decimal, IOP measurement with Goldmann applanation tonometry, corneal ECD assessed with noncontact specular microscopy (Tomey EM-3,000, Tomey, Nagoya).

Group I patients received SLT performed using Lumenis Selecta II (Lumenis, Israel), a Q-switched, frequency-doubled, (Nd:YAG) laser with 534 nm wavelength. The energy level was set at 0.8 mJ and ranged from 0.6 mJ to 1.6 mJ depending on the formation and cavitation of bubbles. The diameter of the laser beam was 400 µm with a duration of 3 ns. The pigmented trabecular meshwork (TMW) was targeted and 100 laser spots were placed circumferential (360°) using a gonioscopic lens. The patients were given apraclonidine 1.0% and topical oxybuprocaine hydrochloride (Conjucain ®) as an anesthetic prior to the procedure.

Group II patients underwent mCPC using IRIDEX CycloG6 laser with a setting of 2,000 mW of 810 nm on a micropulse mode. The probe was applied perpendicular at the limbus with firm pressure, sparing the 3 o'clock and 9 o'clock positions in order to avoid potential damage to the ciliary neurovascular structures. The treatment consisted of an "on-modus" for 0.5 milliseconds (ms) and "off-modus" of 1.1 ms.

No side effects were documented after the mCPC or SLT treatments. The postoperative regimen for group I (SLT) consisted of nonsteroidal anti-inflammatory eyedrops (nepafenac) 3 times daily for 3 days. Posttreatment regimen for group II (mCPC) included topical steroid (prednisolone) prescribed 4 times daily for 1 week and then tapering off to one drop per week. After both procedures (SLT/mCPC) local glaucoma treatment was stopped.

In all patients a noncontact specular microscopy (Tomey EM-4000, Tomey, Nagoya) was performed by the same ophthalmologist (LR) and endothelial cell data was based on the mean value of three consecutive measurements.

Statistical analysis was performed with SPSS software (SPSS Inc, Chicago, Illinois, USA) version 26.0. A significance of $p < 0.05$ was considered for the statistical analysis.

Results

This retrospective, observational study included 40 eyes of 40 glaucoma patients divided into three groups—group I (n = 13) underwent SLT, group II (n = 13) received mCPC, and group III (n = 14) took medical treatment only, comprising of "control" patients age-matched to those in the mCPC and SLT groups. Table 1 summarizes the characteristics and the findings of the included patients.

The mean time interval before and after the treatment was 215 ± 120 days (range: 45–465) in group I (SLT), 273 ± 177 days (range: 96–642) in group II (mCPC), and 209 ± 103 days (range: 74–391) in the control group III (medical treatment only).

Best-corrected Visual Acuity (BCVA)

Mean BCVA in group I (SLT) was 0.83 ± 0.14 at visit 1 and improved tendentially but not significantly (p = 0.059) to 0.89 ± 0.14 at visit 2 after the SLT procedure. The mean BCVA in group II (mCPC) was 0.69 ± 0.30 at visit 1, and 0.84 ± 0.30 at visit 2 after the mCPC procedure, where the change was not significant (p = 0.953). The mean BCVA in group III (control group) was 0.88 ± 0.16 at visit 1 and reduced tendentially but not significantly (p = 0.054) to 0.84 ± 0.16 at visit 2.

Intraocular Pressure (IOP in mm Hg)

Mean IOP for group I (SLT) was 16.1 ± 5.1 mm Hg (range: 9–22) at visit 1 and reduced significantly by 3.5 ± 3.7 mm Hg (p = 0.005) to 12.5 ± 3.3 mm Hg (range: 7–16) at visit 2 after the SLT. The mean IOP for group II (mCPC) was 16.9 ± 3.5 mm Hg (range: 11–24) at visit 1 and decreased significantly by 4.3 ± 4.1 mm Hg (p = 0.003) to 12.6 ± 2.4 mm Hg (range: 10–27) at visit 2 after the mCPC procedure. The mean IOP for group III (medical treatment only) was 12.9 ± 3.7 mm Hg (range: 9–28) at visit 1, and 13.6 ± 4.5 mm Hg (range: 9–19) at visit 2, with no significant change (p = 0.353) in between.

At visit 1, groups I (SLT) and 2 (mCPC) did not differ significantly in terms of the IOP (p = 0.629) whereas group III (control) had a significantly lower mean IOP (group II vs group III, p = 0.008; group I vs group III, p = 0.084). This states that both

Table 1: Demographic data for all included patients and clinical data for all included eyes

		Group I SLT (n = 13 eyes) (n = 13 patients)	*Group II mCPC (n = 13 eyes) (n = 13 patients)*	*Group III Control (n = 14 eyes) (n = 14 patients)*
Female/male		7/6	4/9	4/10
Age (mean) standard deviation (SD)		71.8 ± 8.9	73.8 ± 10.0	74.6 ± 5.9
Right eye/left eye		9/4	5/8	8/6
Observation period (days) (mean ± SD)		215 ± 120	273 ± 177	209 ± 103
BCVA (Visit 1) (decimal)		0.83 ± 0.14	0.69 ± 0.30	0.88 ± 0.16
IOP (mm Hg) ± SD (range) Visit 1		16.1 ± 5.1 (range: 9–22)	16.9 ± 3.5 (range: 11–24)	12.9 ± 3.7 (range: 9–28)
IOP (mm Hg) ± SD (range) Visit 2		12.5 ± 3.3 (range: 7–16)	12.6 ± 2.4 (range: 10–27)	13.6 ± 4.5 (range: 9–19)
ECD (cells/mm^2) (± SD) Visit 1		2409.7 ± 407.2	2104.2 ± 427.6	2107.3 ± 493.3
ECD (cells/mm^2) Visit 2		2355.8 ± 351.1	2017.6 ± 450.9	2067.7 ± 471.0
Lens status	Phakia	8	6	7
	Pseudophakia	5	7	7
	Aphakia	–	–	–
Eyedrops (mean ± SD)		1.46 ± 0.97	1.85 ± 1.35	1.64 ± 1.34

treated groups (group I and II), did not differ from each other at visit 1 in terms of IOP.

Endothelial Cell Density

Mean ECD was 2409.7 ± 407.2 cells/mm^2 in group I (SLT) at visit 1, and 2355.8 ± 351.1 cells/mm^2 at visit 2 after the SLT, where the change of −53.8 ± 114.9 cells/mm^2 was not significant ($p = 0.117$). Mean ECD was 2104.2 ± 427.6 cells/mm^2 in group II (mCPC) at visit 1, and 2017.6 ± 450.9 cells/mm^2 at visit 2 after the mCPC, with an insignificant (p = 0.100) change of −86.6 ± 175.2 cells/mm^2 in-between. Mean ECD was 2107.3 ± 493.3 cells/mm^2 in group III (control group) at visit 1, and 2067.7 ± 471.0 cells/mm^2 at visit 2, where the decrease of −39.6 ± 103.8 cells/mm^2 did not reach statistical significance ($p = 0.177$). From visit 1 to visit 2, the mean relative ECD decrease was 4.0 ± 5.9% for group I (SLT), 2.5 ± 7.0% for group II (mCPC) and 1.0 ± 5.9% for group III (control).

Groups I (SLT) and II (mCPC) did not differ significantly in terms of the IOP decrease after the procedure ($p = 0.690$) nor in the ECD reduction ($p = 0.568$). In both groups (SLT and mCPC) there was no significant correlation between the ECD loss and BCVA or ECD loss and IOP at visit 1 or 2.

Discussion

The corneal endothelium, a structure containing a single layer of hexagonal-shaped cells that work as a cellular pump, is essential to corneal transparency and clear vision. ECD decreases at a rate of 0.6% per year after age 15.[10] Many factors can accelerate this physiological process, especially in glaucoma patients.

In 1997 Gagnon et al. observed lower ECD in glaucoma patients compared to a control group and suggested three alternative theories for this pattern—(1) a direct effect of high IOP on the endothelial cells, (2) congenital alterations of the endothelium and trabecular meshwork, and (3) toxicity of glaucoma medications.[12] However, his last theory, glaucoma medications being toxic for the corneal endothelium could not be proven with scientific evidence. For example, a randomized controlled study of dorzolamide, timolol, and betaxolol eye drops in patients with normal corneas showed no statistically different ECD compared to the baseline. Another study of latanoprost, latanoprost-timolol and timolol revealed a similar pattern with patients showing no significant ECD loss of the medication.[9,13,14] Investigations with a longer follow-up confirmed also these findings.[9]

One contribution of our study is to provide further evidence on the noneffect of glaucoma medications on ECD. In line with past work, our results show that patients receiving medical treatment for glaucoma (group III) did not experience statistically significant ECD loss in the short term with a mean follow-up of 209 ± 103 days ($p = 0.177$).

While there is no evidence for the toxicity of glaucoma medications on ECD, some glaucoma patients still suffer from continued visual field loss in spite of receiving the maximal tolerated levels of glaucoma medications. In such uncontrolled cases, clinicians turn to laser treatments like SLT, and sometimes to surgical interventions such as trabeculectomy and/or tube shunt procedures.

Surgical glaucoma procedures, such as trabeculectomy, Ahmed valve implantation, Baerveldt implantation, and EX-PRESS shunts, while effective, can lead to complications, such as ECD loss.[3,9] For example, a 2 year follow-up study of Ahmed glaucoma valve (AGV) implementation reported 18.6% mean ECD reduction, corroborating earlier work establishing corneal decompensation in 27% of the eyes receiving the procedure.[15,16] Many studies report similar changes in ECD following surgical glaucoma interventions, and yet, we know relatively little on the effects of laser treatments on the corneal endothelium.

Our study aims to fill this gap. We argue that some of the mechanisms that are posited to lead to ECD loss after glaucoma surgery could also be at work following laser treatments such as SLT and mCPC. For example, a cross-sectional study of 40 eyes linked peripheral anterior synechiae (PAS)–caused by inflammation after aqueous shunts–to ECD loss.[17] Another study suggested PAS

might directly harm the corneal endothelial cells by breaking down endothelial barriers and disrupting Na/K-ATPase pumps.[18] We speculate that similar changes might occur after the SLT and mCPC procedures. In support of this idea, one study of 142 eyes with open angle glaucoma reported dark spots in the corneal endothelium in 71 eyes immediately after the SLT.[8] While the dark spots are likely to be transient in normal corneas, the authors noted, such changes might lead to further corneal endothelial compromise in corneas with reduced transparency, or those with pigment deposits am endothelium.

Our design evaluated the changes in ECD and IOP in patients receiving two types of laser treatment (SLT or mCPC) relative to a control group of patients given medical treatment only. Our results showed both treatments (SLT and mCPC) to lead to a statistically significant reduction of the IOP. The literature considers different thresholds (e.g., at least 20 or 30% IOP reduction from baseline) to define "successful" glaucoma treatment.[19] Taking 20% as the threshold, our results indicate both SLT and mCPC to be successful treatments, bringing about 21.7 and 25.4% decrease in IOP, respectively.

Moreover, both SLT and mCPC seem safe for the corneal endothelium. In our data, the SLT patients had higher ECD loss (mean: 4.0 ± 5.9%) compared to the mCPC and medical treatment groups (mean: 2.5 ± 7.0% and 1.0 ± 5.9%, respectively). But, for all three groups, the difference in ECD between visits 1 and 2 remained statistically insignificant.

These results add to a small number of studies in the literature that have evaluated the mCPC procedure. Moussa et al. for example, compared mCPC to continuous wave transscleral cyclophotocoagulation (CW-TCP) and found only the latter to lead to significant histological changes in epithelium or stroma of the ciliary process in cadaveric eyes.[20] However in the same paper, there was no information about the endothelial cells of the cornea. Shah et al.'s earlier work on CW-TCP reported corneal edema in clear grafts among some patients (three out of 19) receiving the procedure.[11]

Our study is the first to show the safety of mCPC for the integrity of corneal endothelium in terms of ECD. While our results indicated a small decrease in ECD in mCPC patients between visits (2.5 ± 7.0%), this difference was not statistically significant. The procedure, therefore, poses no harm to the corneal endothelium.

One limitation of our research was the small sample size and the short follow-up period to observe corneal endothelial damage. Yet, given the limited information in the literature, our findings on the effects of laser treatment modalities on endothelial cells are still crucial and invite clinicians to perform larger and longer-term studies, especially in patients with compromised corneal endothelium.

The main takeaway of our work is that there is no statistically significant ECD loss following mCPC and SLT treatments in the short-term. Yet, more work is certainly needed to assess the effect of these treatments on corneal endothelial cells in the long run.

Compliance with Ethical Standards

All the authors listed above contributed to this project in the design of the work, analysis, interpreting the data, drafting, and revising of the manuscript.

Orcid

Aylin Garip Kuebler https://orcid.org/0000-0002-8676-6781

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