Research Protocol and Statistical Analysis

# Treatment Outcomes of MicroPulse Trans-scleral Cyclophotocoagulation in Uncontrolled Glaucoma
NCT03187418


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Protocol Version: 1.0 (2017-02-14)

Funding: Fonds de recherche en ophtalmologie de l'Université de Montréal (FROUM)

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## Introduction

Glaucoma is a leading cause of irreversible blindness worldwide.[1-2] Adequate control of the intraocular pressure (IOP), which is the only well-established modifiable risk factor in glaucoma, generally allows to prevent significant loss of visual field.[3] Glaucoma treatments are therefore intended to either increase the outflow or decrease the production of aqueous humor in order to reduce intraocular pressure and maintain good visual function. When IOP is difficult to control with medications only, surgical procedures are sometimes required to preserve optic nerve function.[4-5]

Cyclophotocoagulation (CPC) is a type of cycloablation using laser to treat glaucoma. It involves ciliary body destruction by targeting the ciliary epithelium and stroma, resulting in a reduction in aqueous secretion and hence IOP. This strategy is effective for all forms of glaucoma.[6-11]

Traditional trans-scleral cyclophotocoagulation (TSCPC) achieve its cyclodestructive action by using continuous diode laser to target the melanin in the pigmented ciliary body epithelium.[12-14] However, the continuous mode has been shown to cause significant collateral tissue damage to adjacent non-pigmented structures including the ciliary stroma and ciliary muscle. Traditional TSCPC may therefore be associated with serious complications including uveitis, visual deterioration, chronic hypotony, and rarely phthisis bulbi and sympathetic ophthalmia.[15-18] Due to these risks of serious complications and the unpredictability of effect, TSCPC is typically reserved for the treatment of refractory glaucoma or palliation of painful eyes with a very poor prognosis.[19]

More recently, a micropulse delivery mode of diode laser (Micropulse TSCPC, mTSCPC) has been used to treat glaucoma by ablating the ciliary processes and reduce aqueous humor production with more selective targeting and less collateral damage.[13] In contrast to conventional laser delivery where a continuous flow of high intensity energy is delivered, micropulse laser application delivers a series of repetitive short pulses of energy with rest periods in between pulses. This allows energy to build up in the targeted pigmented tissues, eventually reaching the coagulative threshold, while the adjacent non-pigmented structures have time to cool off during the off cycle without reaching the point of coagulation.[20-27]

Only a few studies have described the outcomes of this novel glaucoma therapy, showing mTSCPC to have comparable efficacy with fewer side effects when compared with traditional continuous wave mode diode laser delivery.[13-14,28] This improved side effect profile has the potential to make mTSCPC an earlier therapeutic option instead of reserving it exclusively for end-stage refractory eyes.

## Purpose

The goal of this study is to evaluate the efficacy and safety of the novel form of trans-scleral cyclophotocoagulation using micropulse diode laser and trans-pars plana treatment (Micropulse TSCPC, mTSCPC MP3, IRIDEX CYCLO G6™ Glaucoma Laser System, CA, USA).

The main outcome will be the efficacy of the mTSCPC MP3 evaluated by the short-term and long-term reduction of IOP and number of anti-glaucomatous drops used postoperatively. The other outcomes will be the safety of this device by looking at the possible decrease in corrected distance visual acuity (CDVA), the progression of the optic nerve cupping and the complications.

## Study Design

This will be a prospective, interventional and monocentric study based in a university hospital setting.

Based on the established inclusion and exclusion criteria, the study investigators will enrol patients followed in their own clinic or new patients referred by other ophthalmologists. After learning and asking questions about the risks and benefits of participating in this study, patients will be requested to sign the appropriate information and consent form. They will then have a complete pre-interventional ophthalmologic evaluation including corrected distance visual acuity (CDVA), a complete slit-lamp biomicroscopy examination, an IOP measurement with the Goldmann applanation tonometer, a measurement of the central corneal thickness with a handheld pachymeter (IOPac Advanced, Heidelberg Engineering, Franklin, MA, USA), and a dilated fundus examination with a particular attention to the cup-to-disk ratio (CDR) of the optic nerve.

## Population

A total of fifty (50) glaucoma patients will be included in this prospective study. They will be recruited by two (2) glaucoma specialists at the Notre-Dame Hospital department of ophthalmology (University of Montreal Hospital Center, CHUM). Patients will meet the inclusion and exclusion criteria listed below (Tables 1-2). Participants will undergo a micropulse trans-scleral cyclophotocoagulation (mTSCPC MP3) treatment session in the affected eye.

| **Table 1: Inclusion criteria** |
|---|
| Patients of either sex and any race aged 18 years old and above. |
| Followed by a glaucoma subspecialist at University of Montreal Hospital Center. |
| IOP above target and unresponsive to maximal tolerated medical therapy with or without previous surgical intervention.<br>a. mild glaucoma: IOP > 18 mmHg<br>b. moderate glaucoma: IOP > 15 mmHg<br>c. advanced glaucoma: IOP > 12 mmHg |
| Considered poor candidates for additional filtering surgery or implantation of glaucoma drainage devices. |

| **Table 2: Exclusion criteria** |
|---|
| Patients unable to give informed consent. |
| Patients with significant scleral thinning, defined as thinning of more than one clock hour noticed on scleral transillumination. |
| Ocular infection or inflammation in the study eye in the 2 months prior to enrolment. |
| Intraocular surgery in the study eye in the 2 months prior to enrolment. |

## Baseline Parameters

The following baseline parameters will be recorded for each patient: age, gender, race/ethnicity, type of glaucoma diagnosis, ocular history (previous surgery and laser therapy), preoperative IOP, number of glaucoma medications prior to intervention, preoperative corrected distance visual acuity (CDVA), preoperative cup-to-disc ratio (CDR), pain level (using a verbal analog scale, see Table 3).

| **Table 3: Verbal analog scale for pain level** | |
|---|---|
| *Pain grade* | *Description of pain during laser, after subconjunctival anesthesia* |
| None | No subjective feeling of pain. |
| Mild | Pain easily tolerable. |
| Moderate | Pain tolerable with difficulty. |
| Severe | Pain intolerable. |

## Treatment

The intervention will have to take place within thirty days following the screening appointment and will be executed by one of the two glaucoma specialists listed as the investigators of this study. The procedure will be done under local subconjunctival or rarely retrobulbar anesthesia.

All participants will have a treatment session of micropulse trans-scleral cyclophotocoagulation in the affected eye, using the MicroPulse® P3 Glaucoma Device (MP3) powered by the CYCLO G6™ Glaucoma Laser System (Iridex, Mountain View, CA, USA).

Laser settings will be programmed as follows: power—2000mW-2500mW (average 2000mW) of 810nm infrared diode laser set on micropulse delivery mode; micropulse “on” time—0.5ms; micropulse “off” time—1.1ms; and duty cycle (proportion of each cycle during which the laser is on)—31.33 %.

The laser probe will be applied in a continuous sliding or painting motion from 9:30 to 2:30 and from 3:30 to 8:30. The 3 and 9 o’clock positions will be bypassed to avoid damage to ciliary neurovascular structures, as is standard technique with traditional continuous wave TSCPC. The probe will be applied perpendicular to the limbus with the edge directly on the limbus at all times (fiberoptic tip at 3 mm posterior to the limbus).

The laser will be delivered over 360° for 160–320s. Treatment duration will be adjusted based on iris color and glaucoma severity (mild glaucoma: 160s, moderate glaucoma: 240s, advanced glaucoma: 240-320s).

## Post-Intervention Follow-Up

The patients will be seen by their attending ophthalmologist one (1) week, one (1) month, three (3) months, six (6) months, twelve (12) months and eighteen (18) months after the intervention. They will be seen more often if any complication occurs, in which case the frequency of their visits will be decided by their glaucoma specialist.

The following follow-up parameters will be recorded at each visit: postoperative IOP, number of glaucoma medications, corrected distance visual acuity (CDVA), cup-to-disc ratio (CDR), and presence of complications detected by a complete slit-lamp biomicroscopy examination. The pain level (using a verbal analog scale, see Table 3) will be assessed while performing the laser treatment.

A less than 25% reduction in IOP from baseline after 1 month on two consecutive visits separated by an interval of 1 week will be the basis for a second treatment. The same criteria will apply for third treatment if necessary. Repeat treatments will be done in the same conditions and settings as the primary treatment.

## Primary and Secondary Outcomes

The primary outcome measure of success of this study will be defined as an IOP between 6 and 21 mmHg at final follow-up (18 months) with or without IOP lowering medications, at least 25% reduction in IOP at final follow-up compared to baseline, and no need for incisional glaucoma surgery during follow-up period. The need for a repeat micropulse TSCPC will not be considered a failure.

The secondary outcome measure of success will include the number of repeat treatments, the number of IOP lowering medications at 18 months, changes in CDVA (number of lines reduction or improvement from baseline), the progression of CDR compared to baseline, and the frequency of complications associated with the laser therapy (e.g., prolonged AC inflammation [cells 1+ or higher for more than 2 weeks with topical steroid eye drops], sympathetic ophthalmia, chronic hypotony, phthisis bulbi, scleral thinning).

The outcome of the therapy will ultimately be defined in terms of success rate, hypotony rates, response rates (success and hypotony rates considered together) and retreatment rates.

## Statistical Analysis

Paired 2-tailed Student t-tests will be used to compare changes in IOP, number of glaucoma medications, CDVA and CDR between each time point. For each of these measures, a single factor analysis of variance will be realized. Snellen visual acuities will be converted to logarithm of the minimum angle of resolution (logMAR) values for statistical analysis. Bonferroni correction will be used to control the multiplicity of t-tests. Frequency distribution and percentage will be used for categorical data. Demographic analysis will use Wilcoxon rank-sum test for age and chi-square test for gender. Fisher's exact test will evaluate equivalence of glaucoma types. A level of $p \leq 0.05$ will be considered statistically significant. Analysis will be done with the SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA).

## Benefits, Risks and Disadvantages

Benefits

Micropulse trans-scleral CPC is thought to be an effective strategy to reduce the intraocular pressure in patients who are poor candidates for additional filtering surgery or implantation of glaucoma drainage devices. This therapy is considered less invasive and associated with fewer side effects than the traditional trans-scleral CPC procedure.

By participating in this study, patients will contribute to the research community in the ophthalmology field. The results already published on the micropulse trans-scleral CPC are encouraging, but additional results regarding the efficacy and safety of this procedure will further support its beneficial use.

Risks

Participants are exposed to all conventional complications that may be associated with CPC: prolonged anterior chamber inflammation, sympathetic ophthalmia, chronic hypotony, phthisis bulbi, scleral thinning, decrease in visual acuity, pain. However, the side effect profile of micropulse CPC is thought to be better than conventional glaucoma surgeries and conventional CPC, which has been used for many years in the treatment of advanced glaucoma. In case of failure of micropulse CPC to control adequately the IOP, there is always a possibility to add topical or systemic medication, or to undergo another surgery if needed.

Disadvantages

The only disadvantage in participating in this study will be to come to the requested follow-up appointments, which do not imply any risky or painful procedure.

## Confidentiality

Collected information will only be accessible by the investigators of this study, and only relevant data needed to achieve the scientific objectives of this project will be collected. No identifiable information will be stored in the documents of this study, as patients will be identified solely by a code number. The key of the code linking the identity of the participant to his research file will be retained exclusively by the principal investigator of this project. No nominative information will appear in the final results of this study. Research data may be published or scientifically discussed, but it will not be possible to identify participants.

Data will be stored in the research office of the principal investigator at the CHUM Ophthalmology Department, Notre-Dame hospital, Montreal (Quebec, Canada) on a single password-protected computer device (Removable HDD) for a period of 10 years, and then erased from the device.

## Information and Consent Form

An information and consent form will be signed by all participants. Patients who refuse to participate in this study will have no prejudice and will receive the best standard of care from their attending ophthalmologist.

## Scientific and Ethics Committees

This research project will be reviewed and approved by the CHUM local research ethics committee (CER).

## Budget

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|---|---|
| MicroPulse® P3 (MP3) laser probes reusable for 5 patients each: | |
| 395$/probe x 10 (primary treatment for 50 patients) = 3,950$ | |
| 395$/probe x 5 (for estimated repeat treatments) = 1,975$ | 5,925$ |
| Total…… | |
| Patient recruitment and follow-up require the help of a research assistant for 18 months (part-time)…… | 1,500$ |
| Didactic material (posters, publications, presentations)…… | 1,000$ |
| Statistical consultation…… | 1,000$ |
| Other sources of funding…… | 0$ |
| Total…… | 9,425$ |

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