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PhD THESIS

REDUCTION OF INTRAOCULAR PRESSURE IN CASES OF REFRACTORY GLAUCOMA USING THE TECHNIQUE OF MICROPULSE TRANSSCLERAL LASER CYCLOPHOTOCOAGULATION

– A B S T R A C T –

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SPECIFIC PART

Key words: cyclophotocoagulation, micropulse, glaucoma, bevacizumab, intraocular pressure

The thesis entitled **"Reduction of intraocular pressure in cases of refractory glaucoma using the technique of micropulse transscleral laser cyclophotocoagulation"** is structured in the introductory part, a general part and a specific part. The introductory part mentions some historical facts, the motivation for choosing this topic, and presents o short description of the content of the thesis. The rest of the thesis's structure is presented below.

1. GENERAL PART

1.1. GLAUCOMA INFORMATION AND EPIDEMIOLOGY OF DISEASE

Glaucoma is defined as a group of diseases presenting a common feature, optic neuropathy. Increased intraocular pressure is the main risk factor in glaucoma, but the existence or absence of an increased intraocular pressure does not define this disease. Glaucoma is characterized by the progressive destruction of optic nerve fibers, which are responsible for the transmission of visual information from the eye to the brain.

According to the Romanian Society of Ophthalmology, it is estimated that the number of patients with glaucoma is between 65 and 105 million worldwide. Of these, 10% are currently in the bilateral blindness stage. It is estimated that 7.5 million patients have primary open-angle and angle closure glaucoma, compared to a population of 1.15 billion.

In Romania, there are no official statistics on the number of patients with glaucoma. By correlating with European data, it can be approximated that the number of patients in Romania is approximately 140,000, out of which 132,000 patients with primary open-angle glaucoma.

Treatment options in refractory glaucoma include topical drug therapy with its limitations, classical trabeculectomy intervention, aqueous drainage implants, laser therapies, cyclodistruction / cyclophotocoagulation and the old technique of enucleation or alcohol injections.

1.2. STUDY DESIGN

STUDY PURPOSES AND ORGANISATION

1. Establish a study lot comprising 100 eyes diagnosed with refractory glaucoma and at least one eye treated with local and / or oral treatment for glaucoma.
2. Establish a six-eye refractory glaucoma lot separate from the 100-eye group to evaluate the differences between the mTSCPC technique and the combination of mTSCPC and the subconjunctival bevacizumab injection.
3. Elaboration of inclusion and exclusion criteria.
4. Making a study-adapted informed consent.
5. Obtaining the approval of the ethics committee.

6. Obtaining information about the personal physiological and pathological history and the heredocolateral antecedents relevant to the study.
7. Performing the eye examination, including: testing the visual acuity, intraocular pressure, conducting the biomicroscopic examination of the anterior pole.
8. Grouping the patients according to the initial intraocular pressure, respectively:
    - Group 1 - intraocular pressure < 26 mmHg;
    - Group 2 - intraocular pressure between 26 – 30 mmHg;
    - Group 3 - intraocular pressure between 31 - 49 mmHg;
    - Group 4 - intraocular pressure > 50 mmHg.
9. Depending on the intraocular pressure, laser treatment was performed differently for the 4 groups:
    - Group 1 - 80 s;
    - Group 2 - 100 s;
    - Group 3 - 120 s;
    - Group 4 - 130 s.
10. Applying micro-pulsed transcleral cyclophotocoagulation laser at least in one eye.
11. Measure the intraocular pressure of the treated eye and untreated eye at one week, one month, three months, 6 months, and one-year post laser surgery.
12. Performing a laser treatment or more treatments depending on the intraocular pressure resulting from the first laser treatment.
13. Monitor local treatment with anti-glaucoma drops to eliminate some of them, depending on post-laser intraocular pressure.
14. Conceiving a micropulsed transscleral laser form.
15. Structuring the results to obtain comparative results exemplified by tables, graphs and statistical analysis.
16. To draw conclusions about our experience with mTSCPC.

INCLUSION CRITERIA

1. Positive diagnosis of refractory glaucoma;
2. Age ≥ 18 years old;
3. Signed informed consent by all patients enrolled in the study;
4. Intraocular pressure ≥ 21 mmHg.

EXCLUSION CRITERIA

1. Eye surgery performed over the last 3 months;
2. Eye inflammation;
3. Best corrected visual acuity ≥ light perception.

1.3. INTERNATIONAL STUDIES ON MICROPULSE LASER CYCLOPHOTOCOAGULATION

A reference study for micropulse laser cyclophotocoagulation, conducted by M. Aquino / P. Chew was published in the journal Laser Med Science (Springer - Verlag) in 2017. The study was conducted on 14 patients. The average age was 59.9 years, the mean eye pressure drop was 39%. The number of drugs was reduced from 2.0 to 1.3, an average decrease of 0.7. The success rate was 67%. The evaluation was conducted over a period of 78 months. Laser parameters were 2000 mW / 100 sec (50 sec on each hemisphere).

1.4. CYCLOPHOTODISTRUCTION TECHNIQUES

TRANSCLERAL LASER CYCLOPHOTOCOAGULATION WITH DIODE LASER, CONTINUOS EMMISION

The technique is performed by a solid-state diode conductor, diode laser with a wavelength of 810 nm (Oculight SLx, Iridex Corporation, Mountain View, CA). For laser beam delivery a manual instrument is used, G probe (G probe, Iridex, Mountain View, CA). The laser procedure can be performed in an operating room, the anesthesia being local, retrobulbar or peribulbar. The technique can be applied in two variants. First, the laser is set at the initial power of 1250 mW and lasts 4 seconds, and the maximum power used is 2250 mW. The power of the laser is gradually increased by 150 mW until a sound described as a "pop" is heard. The presence of the sound indicates that there was a tissue explosion in the ciliary process (7). After the sound is heard, the laser power is reduced by 150 mW until the sound disappears. The second variant involves the application of the laser starting at the power of 2000 mW for 2 seconds and gradually decreases until the "pop" sound disappears.

MICROPULSE TRANSCERAL LASER CYCLOPHOTOCOAGULATION WITH LASER DIODE

The technique is made by the same device, the difference being that the laser beam is delivered by the P3 micropulse probe (MP3 probe, Iridex, Mountain View, CA), in a discontinuous way, repetitive short pulses, allowing tissues to cool down between applications, mitigating the side-effects of continuous emission. The laser parameters are: wavelength - 810 nm, power - 2000 mW, application time between 160 and 260 s. The duty cycle is 31.3%, meaning 0.5 ms of transmission and 1.1 ms of pause. The same type of anesthesia, retrobulbar or peribulbar is practiced. The probe is applied by a sliding motion, along the scleroro-corneal limbus, towards the ciliary body, avoiding the meridians of hours 3 and 9, due to the ciliary nerve pathway (9). The micropulsed laser delivery method allows the control of the heating effect of the tissues by fragmenting the continuous laser wave into short, repetitive pulses.

1.5. MICROPULSE TRANSCERAL LASER CYCLOPHOTOCOAGULATION ACTION MECHANISM

Micropulse laser cyclophotocoagulation action is differentiated from the continuous mode by the discontinuous laser wave delivery mode, the duty cycle of the device being 31.3%, which translates to 0.5 ms in which the laser is delivered and 1.1 ms in which the tissue cools down, so that the secondary effects of the continuous form, in the micropulse mode are greatly reduced.

Until recently it was considered that micropulse laser cyclophotocoagulation induced decreased intraocular pressure by increasing the uveoscleral outflow. Recent data from the literature show that it also stimulates the conventional flow through the shrinkage motion it imparts to the ciliary muscle that pulls the trabecular meshwork and the Schlem canal, thus improving conventional outflow (28).

1.6. PARALLEL BETWEEN CONTINUOS LASER CYCLOPHOTO-COAGULATION AND MICROPULSE

Regarding the differences between the two current cyclophoto-coagulation techniques, namely the continuous form and the micropulse form, to compare the two techniques from the point of view of lowering the intraocular pressure, I present below the study on continuous laser cyclophotocoagulation. I have participated to this study and it was the subject of a published scientific paper on cyclophotocoagulation. The results were: the mean intraocular pressure drop in patients treated with continuous laser cyclo-photocoagulation at six months post-laser was around 60%, and in our study on the 100 eyes treated with micropulse laser cyclophotocoagulation the mean drop in intraocular pressure at 6 months and at 1 year was around 40%.

1.7. THE ASSOCIATION BETWEEN MICROPULSE CYCLOPHOTOCOAGULATION TRANSCLERAL LASER AND BEVACIZUMAB

Laser cyclophotocoagulation may also be associated with other methods of lowering intraocular pressure, such as injections of bevacizumab, which is an anti-VEGF agent. No significant difference between the two groups at the time of inclusion ($p = 0.82$) from the point of view of IOP reduction. No significant difference between the two groups at the end of the study ($p = 1$) in terms of IOP reduction. Regression of neovascularization was observed only in the combination therapy group (66.6%).

1.8. TREATMENT OPTIONS IN GLAUCOMA

- Eyedrops
- Laser therapies
  - Argon laser trabeculoplasty or Nd: YAG laser selective trabeculoplasty,
  - Nd: YAG laser iridotomy
  - Laser Iridoplasty
  - Diodes laser cyclophotocoagulation with the two continuous or micropulse modes
- Trabeculectomy

1.9. ANATOMY AND PHYSIOLOGY

The eyeball is a neurosensory organ that provides the visual function and is responsible for providing approximately 90% of the information in the environment (34). The anteroposterior axis of the eyeball has a length of about 24 mm. The eyeball is located at orbit level and is covered by a layer of connective tissue called the Tenon capsule, a fine membrane that covers the eyeball from the corneal-scleral junction to the optic nerve and delimits it from the orbital fat, allowing it to rotate freely.

The structure of the eyeball consists of the walls of the eyeball (the inner tunic - the tunic, the medial tunic and the outer tunic - the sclera) and the transparent, refractive medians (from the anterior towards the posterior of the cornea, the aqueous humor, the crystalline, the vitreous body). Anatomical structures also describe the annexes of eyeballs containing: eyelids, eyebrows, eyelashes, lacrimal apparatus and extraocular muscles.

2. SPECIFIC PART

2.1. STUDY PURPOSE

The aim of the study is to reduce intraocular pressure in patients diagnosed with refractory glaucoma using the micropulsed transcleral cyclophotocoagulation laser technique.

2.2. THE OBJECTIVES OF THE STUDY

The proposed objectives include: primary objectives: determination of the success rate of the micropulsed transscleral cyclophotocoagulation laser treatment; determination of the intraocular pressure after mTSCPC application, one week, one month, three months, six months and one year; tracking stability of results for 12 months post laser. Secondary endpoints: number of antiglaucoma drops used after the laser procedure, number of laser procedures performed, reduction of iris neovascularization, evaluation of pain experienced by the patient during the laser procedure. Tertiary objectives: visual acuity assessment, assessment of possible inflammatory reaction in the anterior chamber, identification and management of complications.

2.3. MATERIAL AND METHOD

LOT AND STUDIED GROUPS

The study is a non-comparative, prospective, interventional and with consecutive enrollment of patients with refractory glaucoma who have signed a written consent to participate in this scientific experiment. The study was conducted between 2016 and 2018. A total of 100 eyes with high intraocular pressure were subjected to micropulsed transscleral laser cyclophotocoagulation. All subjects had at least one laser-treated eye in one or more sessions (maximum 3). Three of the subjects had both eyes undergoing laser treatment. The evolution of the intraocular pressure of both eyes was monitored over a 12-month period at pre-established times: one week, 1 month, 3 months, 6 months, and a final visit at 12 months.

I also made up a six-eye batch separate from the 100-eyes batch. We used the same inclusion and exclusion criteria. This six-eye batch was divided into two groups. The first group of three eyes were treated with the mTSCPC technique. The second batch of three eyes were treated with the association between mTSCPC and subconjunctival bevacizumab. All patients enrolled in the study received topical post laser treatment with prednisolone acetate 1%, netilmicin and cyclopentolate for 4 weeks, which were added to their chronic anti glaucomatous treatment.

STATISTICAL ANALYSIS METHODS

The statistical analysis was performed using R version 3.5.0. The statistical tests used in this study were:

- t-Student (t-test) test, Mann-Whitney, Shapiro or Kolgomorov-Smirov; the Welch test; Wilcoxon rank sum test, Kruskal-Wallis (unpaired date), Friedmann (pair data), chi-square or Fischer tests.

2.4. RESULTS

DEMOGRAPHIC AND STRUCTURAL RESULTS

Figure 1 shows the distribution of intraocular pressure (mmHg) in the initial sex-based visit for the two treatment groups (mTSCPC + drug versus drug) in the boxplot form:

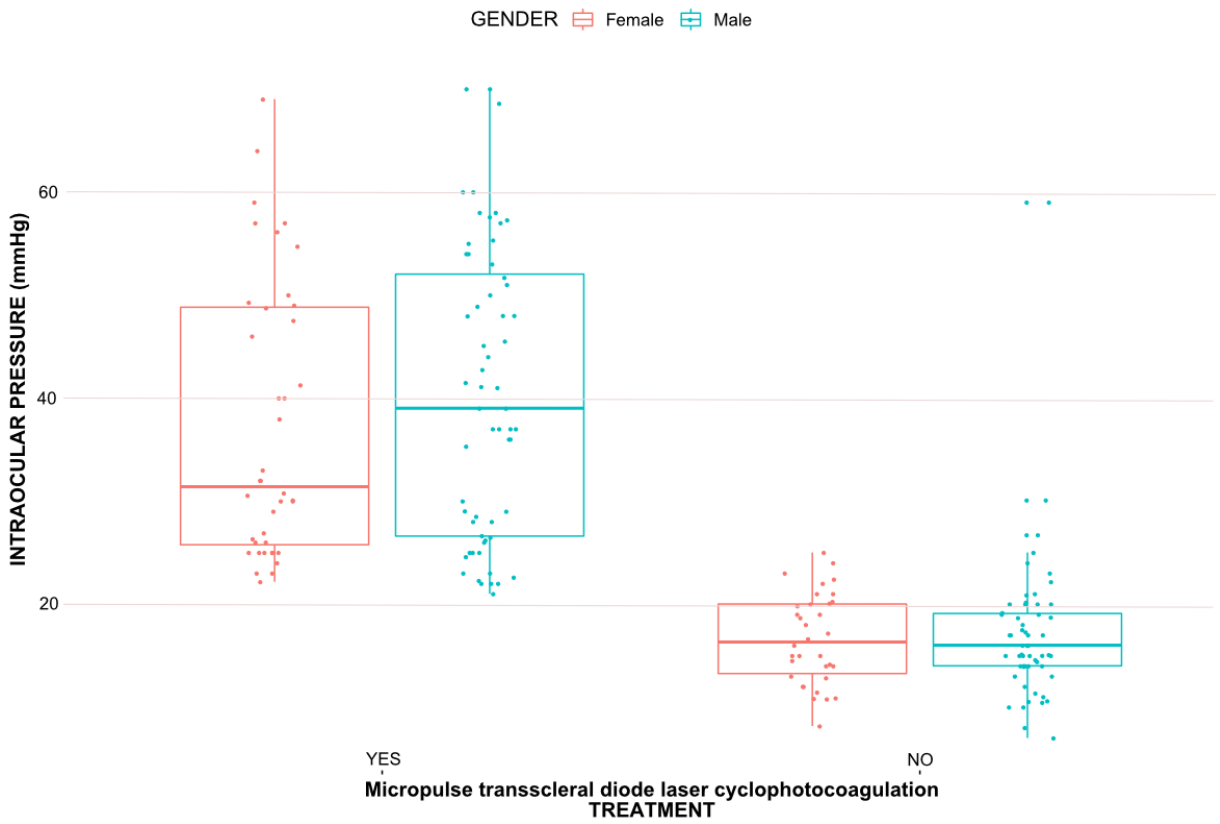

Figure 1. Boxplot of distribution of intraocular pressure values mmHg) at baseline visit for patients who received mTSCPC treatment or non-invasive techniques based on gender

Table 1 Patient's demographic data

VARIABLE	CATEGORY	N	%	MEAN	DEV. STD.	MEDIAN	MIN	MAX	95%CI	95%CI
Age	Women	31	31.96	63.52	13.69	66	23	85	58.49	68.54
	Men	66	68.04	61.58	11.38	79	30	90	58.78	64.37
	Total	**97**	**100.0**	**62.20**	**12.13**	**60**	**23**	**85**	**59.75**	**64.64**
Race	Caucasian	97	100.00							

* CI = Confidence Interval
** no data acquired for one eye

PRIMARY RESULTS

SUCCESS RATE

The success of the experiment was defined as a decrease of at least 30% of the intraocular pressure or keeping the IOP in the range of 6 - 21 mmHg, 12 months after the first session. The success rate is therefore the ratio of the number of successful cases reported to the total number of cases (100).

INTRAOCULAR PRESSURE EVOLUTION

The average ± standard deviation of the intraocular pressure of the laser-treated eyes (22.76 ±8.14 mmHg) was found to be close to the 21 mmHg (arguably considered) normal value. None of the two groups exhibit a normal distribution of PIO values: $p < 0.001$ (Shapiro test) in both cases. The 12-months decrease in PIO values for the group of eyes treated with mTSCPC, from 39.14 ±13.84 mmHg to 22.76 ±8.14 mmHg, is statistically significant (Wilcoxon pair data, $p < 0.001$).

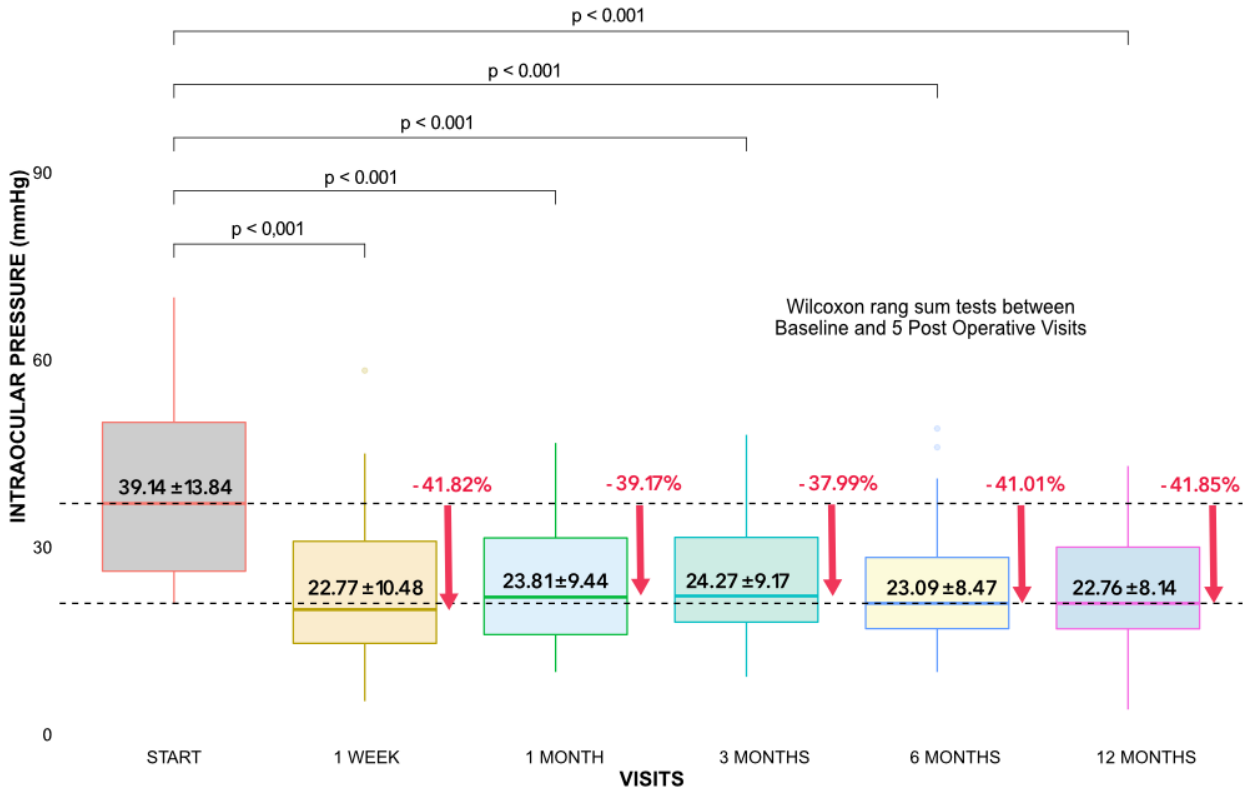

Figure 2 Intraocular pressure by visit

RESULTS STABILITY THROUGHOUT THE STUDY

Throughout the study, mean fluctuations in the mean intraocular pressure were minor. After an insignificant statistical increase at 3 months (Wilcoxon test, $p > 0.050$) versus the PIO postoperative mean, the pressure stabilized at 12 months.

SECONDARY RESULTS

NUMBER OF ANTIGLAUCOMA DROPS USED AFTER THE LASER PROCEDURE

The number of drops decreased from 2.63 to 1.78.

EVALUATION OF THE PATIENT RESPONSE TO PAIN DURING THE LASER PROCEDURE

An average score of 58.63 mm on the VAS scale is observed for the entire sample of 100 patients, corresponding to moderate pain.

NUMBER OF LASER TREATMENT

The average laser treatment number was 1.26.

REDUCTION OF IRIS NEOVASCULARIZATION

In the group treated with the association between mTSCPC and subconjunctival bevacizumab, both intraocular pressure and iris neovascularization decreased.

TERTIARY RESULTS

- Decrease visual acuity after laser in 5 eyes;
- 30 eyes have experienced inflammatory reactions that resolved within 1 month;
- Identification and management of complications.

OTHER RESULTS

The decrease of the intraocular pressure in the group treated with TSCPC was approximately 60% and in the mTSCPC group was approximately 40%.

2.5. DISCUSSIONS

Micropulse transscleral laser cyclophotocoagulation is a non-invasive, repeatable, easy-to-use laser procedure that has been shown to be successfully when used to lower intraocular pressure. The parameters monitored in our study are the following:

- The success rate of our study was 79%;
- The mean decrease in intraocular pressure was 41.85% after one year;
- The average of treatments performed was 1.26;
- The number of medications administered decreased by 32% from 2.63 to 1.78.

Another reference study for micropulse laser cyclophotocoagulation was conducted by M. Aquino / P. Chew in the journal Laser Med Science (Springer-Verlag). The study was conducted in 14 patients over a period of 78 months, reporting the following results:

- the success rate was 67%;
- eye drop pressure was 39%;
- the number of drugs was reduced from 2.0 to 1.3, an average decrease of 0.7 (-35%).

2.6. CONCLUSIONS

1. The success rate in our study was 79%, being in line with the success rates published in the literature.
2. Decrease in intraocular pressure was 41.85% at 12 months, the results being satisfactory and stable for one year.
3. The association between mTSCPC and bevacizumab reduced iris neovascularization, but the decrease in intraocular pressure was similar in both groups (34.33 ±3.06 mmHg versus 34.33 ±3.52 mmHg).
4. Complications recorded in this study were 3 cases of ocular hypotonia (PIO <6 mmHg), 5 cases of visual acuity decrease and 30 eyes with an inflammatory reaction of the previous chamber.
5. The average decrease in intraocular pressure in patients treated with TSCPC at 6 months was around 60%, and in our study on the 100 mTSCPC-treated eyes, the mean decrease in intraocular pressure at 6 months was around 40%.
6. Decrease of the number of drops administered from 2.63 to 1.78 (-32%).
7. The average number of treatments was 1.26.
8. The result of the pain assessment experienced by the patient during the laser procedure was performed by using the VAS scale and the results corresponded to a mean pain.

2.7. PERSONAL CONTRIBUTIONS

1. Our study demonstrates a presional decrease of 41.85% and brings a scientific contribution that supports the hypothesis, little studied, where the uveoscleral pathway is not the only method of lowering pressure after transscleral cyclophotocoagulation laser treatment.
2. Our study comprised a batch of 100 eyes treated with the mTSCPC technique followed for one year, being the largest study in literature
3. Our paper on the association between micropulsed laser cyclophotocoagulation and subconjunctival bevacizumab injection is a unique and original publication.
4. Conceiving a micropulsed transscleral laser form.
5. Subdivision of the 100 eyes group into four groups, depending on the pressure measured at the time of study enrollment.
6. Establishing the time of application of the laser according to the intraocular pressure value.
7. Using the pain monitoring scale to evaluate the pain experienced by the patient during the micropulsed transscleral laser cyclophotocoagulation procedure.