The Efficacy and Safety of Diode Laser Cycloablation in the Treatment of Refractory Glaucoma in a South African Population

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DECLARATION

I declare that this thesis is my own work in design and execution and I have not submitted it, in its entirety or in part, in any previous application for a degree or qualification at this or any other university or institute of learning.

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April 2022

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Aim

The development of a safe and effective protocol for trans-scleral cyclophotocoagulation in a Southern African population presenting with refractory glaucoma to a tertiary eye care centre.

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Results

119 eyes of 105 eligible patients were treated during the study period. The mean laser power was 1766 ± 187 milliwatt per burn for a mean of 15.6 ± 2.9 burns per eye. Mean total delivered energy per eye was 55.28 ± 12.61 Joule. 64% of the patients who followed up for the entire six-month period had an intraocular pressure reduction of ≥ 30% and 42.2% of those followed up had an IOP of ≤ 22 mmHg. The pain scores reported by patients decreased significantly between pre-operatively and three months (coefficient -1.752, $p<0.001$) and between pre-operatively and six months (coefficient -1.498, $p=0.002$). There was not a statistically significant effect on the change in topical medication from pre-operatively to three months (coefficient = -0.089, $p=0.186$), nor from pre-operatively to six months (coefficient = -0.003, $p=0.946$). Oral acetazolamide use decreased from 50.4% of patients at the date of their initial cyclophotocoagulation treatment to 9.3% at three months and further to 7.8% at six months. One eye had a scleral perforation at the time of initial treatment; no further complications arose.

Conclusion

An individualized, “pop-titrated” cyclophotocoagulation protocol is safe and effective for use in a Southern African population. Retreatment should be considered at three months if intraocular pressure is not adequately controlled.

OPSOMMING

Doelwit

Die ontwikkeling van ‘n veilige en effektiewe protokol vir trans-sklerale siklofotokoagulasie in ‘n Suider-Afrikaanse bevolking wat presenteer met onbeheerde gloukoom by ‘n tersiêre oogsorgsentrum.

Metodiek

‘n Prospektiewe, nie-gerandomiseerde, observasionele studie van pasiënte by die Tygerberg Hospitaal oogkliniek, Kaapstad, Suid-Afrika tussen Maart 2018 en Januarie 2020

Resultate

119 oë van 105 pasiënte was behandel gedurende die studieperiode. Die gemiddelde laser-energie was 1766 ± 187 milliwatt per laseraanwending vir ‘n gemiddeld van 15.6 ± 2.9 aanwendings per oog. Die gemiddelde energie toegepas per oog was 55.28 ± 12.61 Joule. 64% van pasiënte wie opgevolg het vir die ses-maand periode het ‘n intraokulêre druk verlaging van ≥ 30% en 42.2% van diegene het ‘n drukverlaging tot ≤ 22 mmHg gehad. Die pyntellings gerapporteer deur pasiënte het noemenswaardig verminder van pre-operatief en drie maande (koëffisiënt -1.752, $p<0.001$) en tussen pre-operatief en ses maande (koëffisiënt -1.498, $p=0.002$). Daar was nie ‘n statisties beduidende verandering in die gebruik van topikale medikasies tussen pre-operatief en drie maande (koëffisiënt = -0.089, $p=0.186$) of ses maande nie (koëffisiënt = -0.003, $p=0.946$). Orale asetazolamied verbruik het verminder vanaf ‘n vlak van 50.4% van pasiënte by aanvanklike behandelingsdatum tot 9.3% op drie maande en verder tot 7.8% op ses maande. Een oog het ‘n sklerale perforasie ontwikkel na laserbehandeling maar geen verdere komplikasies is gedokumenteer nie.

Gevolgtrekkings

'n Geïndividualiseerde, "pop-titrated" siklofotokoagulasie protokol is veilig en effektief vir gebruik in 'n Suider-Afrikaanse bevolking. Herbehandeling behoort oorweeg word op drie maande indien intraokulêre druk nie voldoende beheer is nie.

1. INTRODUCTION

1.1 Background

Cyclodestructive procedures have become well-established in the treatment of refractory glaucoma since their inception in the 1930s.[1,2] These interventions coagulate or ablate the ciliary body epithelium, thereby reducing the production of aqueous humor and, by extension, intraocular pressure (IOP).[3] Initial developments in this field included cyclectomy (surgical excision of the ciliary body), cyclodiathermy, and cyclocryotherapy.[4] Due to complication rates and limited clinical efficacy these earlier modalities have largely been superseded by cyclophotocoagulation (CPC) through the application of micropulse or continuous-wave laser energy to the ciliary body, either trans-sclerally (trans-scleral cyclophotocoagulation; TSCPC), transpupillary or endoscopically (endoscopic cyclophotocoagulation; ECP).[1,3] While initial laser CPC treatments used ruby laser (693 nm wavelength), current modalities are mainly neodymium:yttrium-aluminium-garnet (Nd:YAG; 1064 nm) and infrared semiconductor diode lasers (810 nm).[1,3,4] The safety profile of TSCPC offers improvements over those of the earlier cyclodestructive procedures but serious complications may still occur.[5,6] These include but are not limited to: severe or prolonged iridocyclitis, hyphaema, hypotony, persistent mydriasis, scleral perforation, phthisis bulbi, and sympathetic ophthalmia. [1,3,4] CPC has been widely used for cases of refractory glaucoma[5,7,8] or intractably painful glaucomatous eyes[9] with very poor or no visual prognosis, but as more data have become available TSCPC and ECP have become more frequently used in eyes with good visual prognosis [10,11] and are in some cases considered for first-line surgical treatment in glaucoma.[12] Since the absorption of laser energy and the subsequent thermal coagulative necrosis is influenced by the amount of melanin present in the ciliary body[13], various combinations of total laser burns, degrees of ciliary body treated[14], laser power and laser duration[15] have been proposed for population groups with varying amounts of ocular pigment. [16–22] Furthermore, because the response to treatment may be influenced by the type of glaucoma[23–25] and method of laser application[26] it may be prudent to tailor each treatment to the individual patient.[27,28]

1.2 Research problem statement

Data on the treatment of refractory glaucoma in African population groups reveal varied approaches to energy delivery and number of clock hours treated.[12,18,19,29] There is a paucity of data from African and specifically Southern African patients regarding TSCPC and its success and complication rate.

1.3 Aim and objectives of the study

Our aim was to develop a safe and effective protocol for TSCPC in a Southern African population presenting to our eye clinic with refractory glaucoma.

1.3.1 Primary objectives:

To determine and refine the laser energy settings and treatment parameters for TSCPC for the best IOP control in eyes with refractory glaucoma, while minimizing potential adverse effects in our patient population. Treatment success was defined by a reduction in IOP to ≤ 22mmHg or a ≥ 30% reduction from baseline IOP.

1.3.2 Secondary objectives:

To assess: 1) reduction in ocular pain scores, 2) reduction in the number of topical anti-glaucoma medications and 3) reduction in the use of oral acetazolamide for IOP control over time.

2. RESEARCH METHODOLOGY

2.1 Study design

This prospective, non-randomised, observational study was undertaken in patients attending the Eye Clinic at Tygerberg Hospital, Cape Town, South Africa between March 2018 and January 2020.

2.2 Inclusion and exclusion criteria

The study cohort met the following inclusion criteria:

(a) Age ≥ 18 years

(b) CPC-naïve

(c) primary or secondary glaucoma not controlled on maximal medical treatment (refractory glaucoma) and who had failed or declined surgical intervention

(d) patients with refractory glaucoma and poor visual potential who would not be considered candidates for filtration surgery

(e) painful, blind eyes with raised intraocular pressure.

Patients with the following characteristics were excluded from the study:

(a) Age <18 years

(b) normal IOP

(c) phthisis bulbi or

(d) previous CPC

2.3 Data collection

After obtaining informed consent, the following data were collected:

(a) demographic data (age, sex)

(b) pre-treatment Goldmann applanation IOP

(c) type of glaucoma

(d) current anti-glaucoma medications

(e) indications for TSCPC (painful or painless refractory glaucoma; pain graded as none [0], mild [1], moderate [2] and severe [3])

(f) total laser energy delivered (total energy [Joules, J] = number of burns x duration of burns [seconds] x power [Watt])

(g) area and extent of ciliary body treated

(h) post-treatment medications

2.4 CPC Procedure

The TSCPC was performed with a Nidek 3300 diode laser system (Nidek Co., Ltd., Aichi, Japan), using a 20-gauge straight probe. Patients received modified peribulbar anesthesia and 5% povidone iodine ocular surface preparation. A wire speculum was used to separate the eyelids and the ciliary body was identified using transillumination with Finoff transilluminator. Using a protocol based on publications reporting the use of lower power TSCPC in darker pigmented irides, laser was applied to the inferior 180° of the ciliary body with the probe at 90° to the surface[14,21,30]. A maximum of eight burns per quadrant were performed, avoiding the three and nine o'clock positions where the long ciliary nerves are located. The laser duration was fixed at two seconds per burn and power started at 1500 milliwatt (mW) and increased in 150 mW increments until a barely-audible "pop" was noted, following which the rest of the burns were completed at the same energy. Subconjunctival dexamethasone 4mg was administered at the end of the laser procedure and the patient was discharged on their current anti-glaucoma medications as well as oral paracetamol and ibuprofen and topical dexamethasone 0.1% four times daily and atropine 1% twice daily for one to two weeks. Follow-up visits were scheduled for 6 weeks, 3 months and 6 months after the laser treatment.

2.5 Follow-Up

At follow-up, patients' visual acuity, IOP, anti-glaucoma medications, slit lamp examination findings and complications were recorded. To minimize the risk of hypotony, repeat CPC was not recommended during the first three months. If further TSCPC was required, the first repeat was performed as for the initial laser treatment on the inferior 180° and subsequent laser on either of the superior quadrants for 90° only. Data was collected in a Microsoft Excel spreadsheet and analyzed in IBM SPSS (Chicago, IL, USA).

2.6 Statistical analysis

Although participants were followed up for varying amounts of time, we identified the visits closest to their three-month and six-month post-operative dates, and used three time points, namely pre-operative, three months and six months for comparison of outcomes over time in those who had data available at these time points. Data for each eye was analyzed separately, even when patients had both eyes treated, and longitudinal modelling was achieved using Generalized Linear Models (GLM) which adjusted for the repeated measures within patient of eye being treated (1 or 2 eyes per patient) and time (1 to 3 time points per patient). An unstructured correlation matrix was specified. For continuous, normally distributed outcomes like IOP, a normal probability distribution was specified with an identity link function. For count outcomes like number of medications, a Poisson distribution was used with a log link function. For ordinal variables like pain (4 ordinal levels) a multinomial distribution was used with a cumulative logit link. The GLM included all data available at each time point. The independent variable of interest in each model was the main effect of time, where pre-op was the reference time point. Three months and six months relative to pre-op were tested and coefficients or exponentiated coefficients and p-values from the models were reported.

2.7 Ethical considerations

Human Ethics Research Council approval was obtained (Stellenbosch University Ethics Reference number S15/10/244:). Patients entered the study voluntarily after informed consent was obtained. The study was performed in compliance with the principles of the Declaration of Helsinki.

3. RESULTS

3.1 Demographic data

In total, 119 eyes of 105 eligible patients were treated during the study period. Demographic data and the different diagnoses are shown in Table 1. Forty-nine eyes were treated due to painful, refractory glaucoma and 70 for painless uncontrolled IOP. The mean baseline IOP measurement was 44 ± 10.7 mmHg. Ciliary body pigmentation may have varied depending on the ethnic background of the patients seen at the eye clinic, but no official or self-identified racial details were recorded in the patients' hospital registration details or clinical notes.

Table 1 – Patient Characteristics

Gender	No (%)
Males	60 (57.1)
Females	45 (42.9)
Age (years)	
Mean ± SD	57 ± 11.9
Range	18-88
Diagnosis	
NVG	75 (63.0%)
POAG	17 (14.3%)
CACG	10 (8.4%)
Trauma/Angle Recession	11 (9.2%)
PXG	3 (2.5%)
Post-PPV	2 (1.7%)

Uveitic glaucoma	1 (0.8%)

(NVG, neovascular glaucoma; POAG, primary open angle glaucoma; CACG, chronic angle closure glaucoma; PXG, pseudoexfoliation glaucoma; Post-PPV, post-pars plana vitrectomy)

3.2 Pre-Treatment Medication Use

Prior to treatment, 55 patients (52.38%) were receiving oral acetazolamide for IOP control. The topical anti-glaucoma medications available to the patients are brimonidine tartrate 0.15% (Alphagan® [Allergan, inc.]), timolol 0.5% or levobunolol 0.5% (Betagan® [Allergan, inc.]), bimatoprost 0.03% (Lumigan® [Allergan, inc.]) and dorzolamide 2% (Glaucopress® [Actor Pharma]). These are available both as single drug preparations and in fixed combinations (Combigan® and Ganfort ® [Allergan, inc.]), Glaumide-Co ® [Actor Pharma]); no distinction was made between preparations used. At baseline, 102 eyes were receiving brimonidine, 106 timolol, 94 bimatoprost and 12 dorzolamide. The median number of topical medications was 3 per treated eye [interquartile range (IQR) = 2-3]).

3.3 TSCPC Characteristics

Each patient had TSCPC to the inferior 180° at the initial treatment visit. The mean laser power was 1766 ± 187 mW per burn for a mean of 15.6 ± 2.9 burns per eye. Mean total delivered energy per eye was 55.28 ± 12.61 J. In total, 14 doctors were involved in administering the TSCPC to patients over the study period. At the discretion of their treating physician, nine eyes of nine different patients received a second TSCPC treatment with a mean power of 48.60 ± 16.94 J between three and six months after the initial TSCPC. Of the re-treated eyes, four had angle recession, two had NVG and one each had POAG, post-PKP glaucoma and post-PPV glaucoma.

3.4 IOP Reduction

Of the 119 treated eyes, 74 were seen at the three months visit and 64 at the six months mark. IOP decreased to a mean of 25.49 ± 12.77 mmHg (95% CI 23.12 – 27.87) at three months and 25.31 ± 12.32

mmHg (95% CI 22.29 – 28.33) at six months . Regarding the specified criteria for successful IOP reduction, 64% of the patients who followed up for the entire six-month period had an IOP reduction of ≥ 30% and 42.2% of those followed up had an IOP of ≤ 22 mmHg (figure 1). The decrease in mean IOP between pre-op and three months was 17.81 mmHg (p<0.001) whereas the difference in mean IOP between pre-op and six months was 19.28 mmHg (p<0.001).

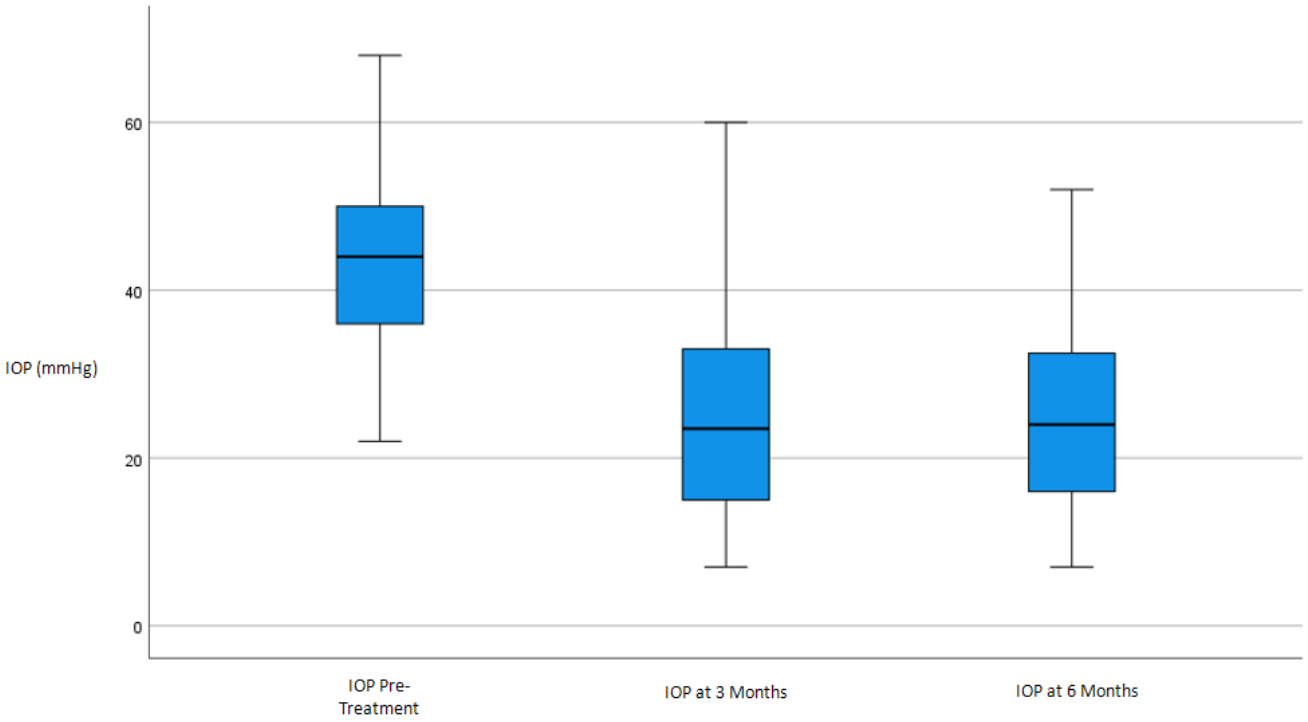

Figure 1 – Box and whisker plots showing distribution of intraocular pressure over time. Vertical bars denote range.

3.5 Pain Reduction

Pain score reduction at three and six months compared with pre-op showed a decrease (figure 2). The pain scores decreased significantly between pre-op and three months (coefficient -1.752, p<0.001) and between pre-op and six months (coefficient -1.498, p=0.002).

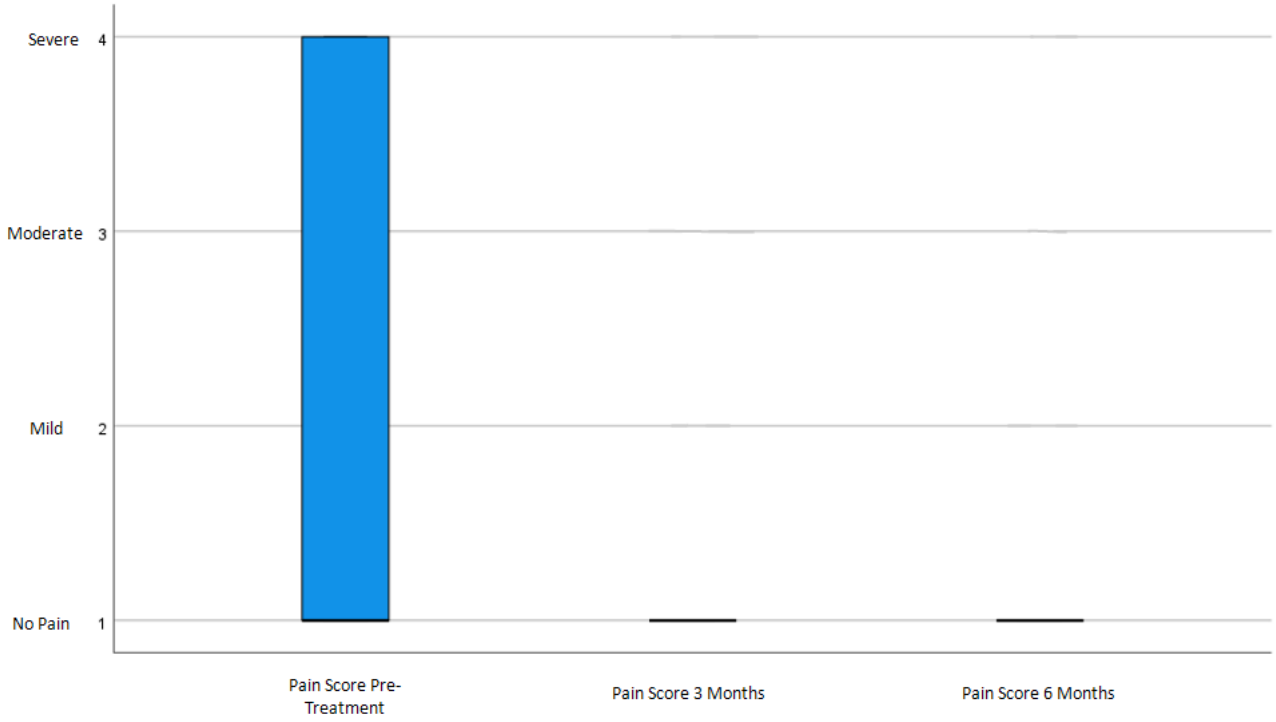

Figure 2 – Decrease in pain score over time

3.6 Topical Medication Use

Topical anti-glaucoma medication use remained at a median of 3 drugs per treated eye (IQR = 2 - 3) at three months and decreased to 2 drugs per eye at six months (figure 3). The effect of the change in topical medicine from pre-op to three months was not statistically significant (coefficient = -0.089, p=0.186) and neither was the change from pre-op to six months (coefficient = -0.003, p=0.946). This is reflected in Figure 3 which shows much overlap between the distributions of number of topical medications at each time point.

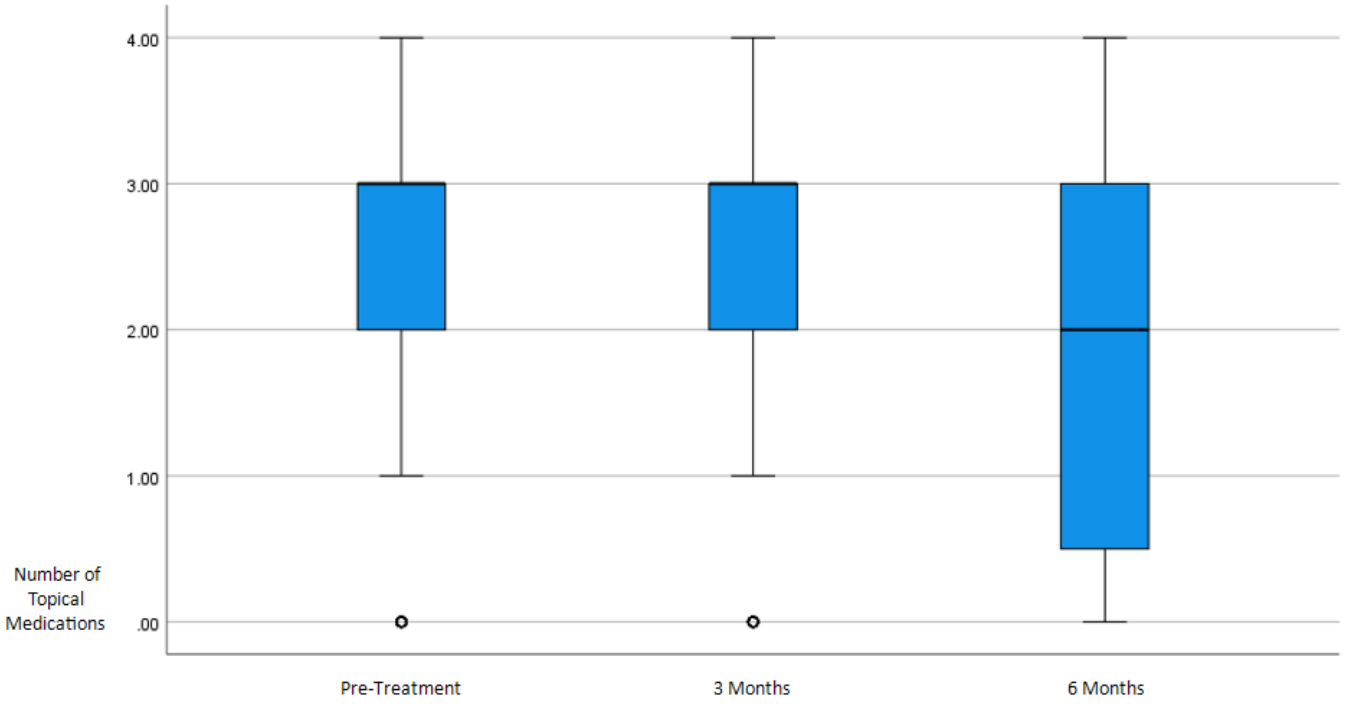

Figure 3 – Box and whisker plots of decrease in topical medication use over time

3.7 Oral Medication Use

Oral acetazolamide was used by 50.4% of patients at the date of their initial CPC treatment. This decreased to 9.3% of patients still using oral acetazolamide at 3 months and further to 7.8% of patients followed up at 6 months.

	Using	Number of patients
Oral Acetazolamide - pre-treatment	yes	60
	no	59
		119
Oral Acetazolamide - 3 months	yes	7
	no	68
		75
Oral Acetazolamide - 6 months	yes	5
	no	59
		64

Table 2 – Oral acetazolamide use over time

3.8 Complications

None of the eyes that received TSCPC developed hypotony or phthisis bulbi during the follow-up period. No other transient complications were noted; however, one patient with high myopia and longstanding raised IOP post-PPV had a scleral perforation from the diode handpiece during application of one of the laser burns. This was repaired with a scleral patch graft in theatre and no further complications arose.

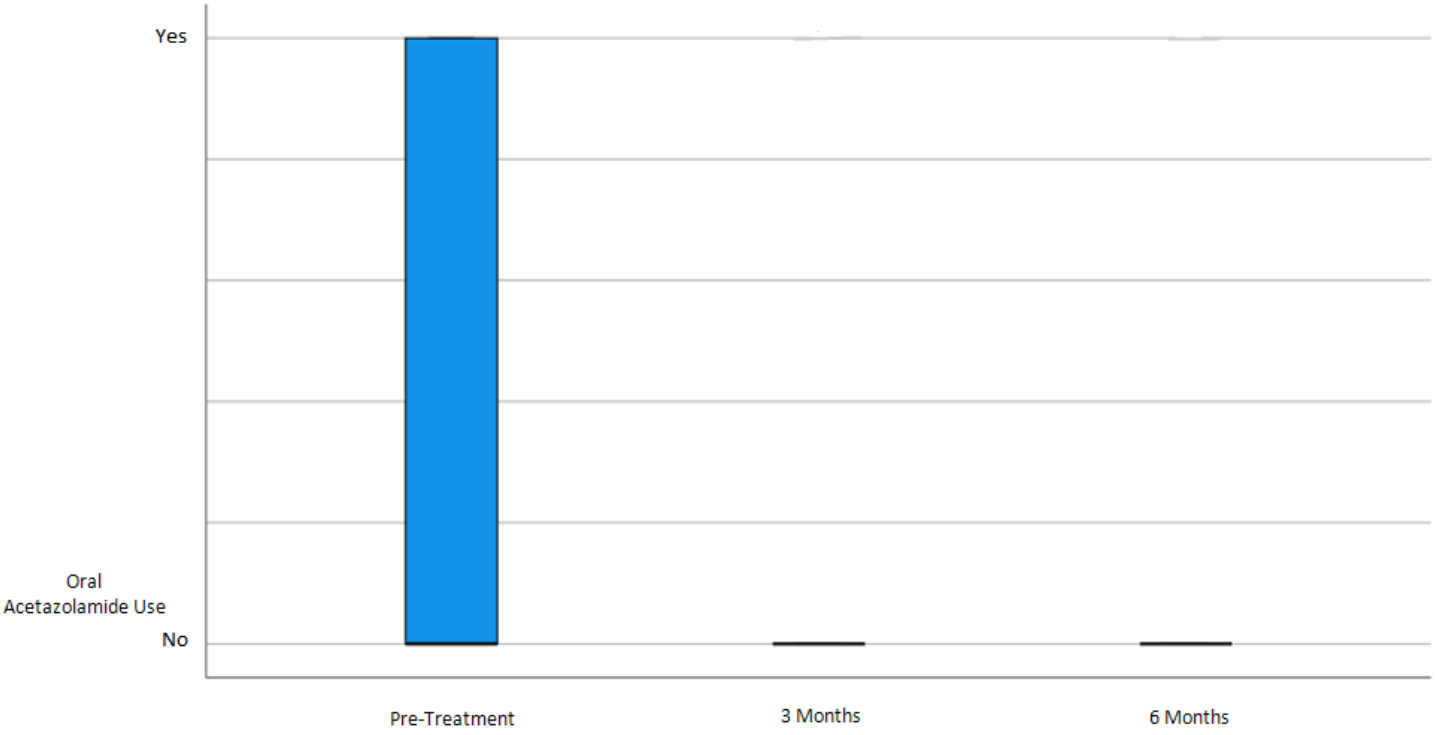

Figure 4 – Change in number of patients using oral acetazolamide over time

4. DISCUSSION

In our patient group undergoing TSCPC, IOP was successfully reduced by ≥ 30% in 64% of patients followed up at 6 months and an IOP of ≤ 22 mmHg was reached in 42.2% of patients over the same period. Published TSCPC success rates in other population groups with increased ciliary body pigmentation have been noted to fall between 48% and 78% [14,16,21,28]; however, there are minor differences in the values that defined successful treatment in the various studies cited.

The re-treatment rate in our study was 7.56%, compared to values as varied as 15.4%[21], 25%[21], 32.9%[16], 42%[7] and 55%[7]. Laser energy delivered in our study was 55.28 ± 12.61 J, which compared favorably with other studies that ranged from 47.0 ± 9.4 J to 155.2 J [7,16,21]. The protocol used for the TSCPC in this study limited the initial treatment to 16 burns on the inferior 180° of the ciliary body; other protocols show wide variation in the number of laser burns and degrees treated at the initial visit – from 10 to 55 burns or more and from 180° to the full 360° [7,16,21,27,28].

Similar effects on pain reduction were seen as in other studies – near universal pain relief at follow-up. Reduction in topical anti-glaucoma medications did not reach a statistically significant level, but the number of patients using oral acetazolamide reduced to 7.8% at six months. Similar studies have managed to decrease anti-glaucoma medication levels by between 19.5 to 52.6% and greater [7,16,21,27,28].

The complication rate in our study was 0.84%. Rates of complications after TSCPC in the literature range from 7.1% to 12% [3,16]. Not all publications elaborate on the type and severity of complications, however. Hypotony (IOP ≤ 6 mmHg) and phthisis bulbi are most often mentioned, but transient complications such as conjunctival burns may also be included in overall complication rates. The direct correlation between greater amounts of energy delivered and higher rates of complications has been well described in the literature [2,15,21]. Similar studies using an individualised “pop-titrated” and limited area of ciliary body (180° or less at initial treatment) appear to have lower rates of complications and vision loss at the cost

of more repeat treatments and slower decrease in medication use [21].

5. LIMITATIONS OF THE STUDY

The study was limited by the following factors:

1. Poor patient follow-up – only 64 of 119 (53.7%) completed the 6-month follow-up
2. The TSCPC was not performed by a single individual but by 14 different doctors; this does however reflect normal clinic operations
3. Patients enrolled in the study in the latter half of 2019 had their follow-up visits curtailed by COVID-19 and related lockdown measures.
4. Repeat laser treatment was recommended and given at the discretion of the patient's treating physician and was not applied in a standardized fashion to all patients at follow-up.
5. Patient skin pigmentation was not recorded and should be in future studies to determine whether different outcomes are achieved in patients who are naturally less or more pigmented.

6. CONCLUSION AND RECOMMENDATIONS

Individualized, pop-titrated TSCPC in a Southern African patient population using energy settings in the lower range of those used in other population groups with similarly pigmented ciliary body structures is a safe and cost-effective method of managing refractory glaucoma and painful blind eyes. Patient dependency on anti-glaucoma medications, particularly oral acetazolamide, can be diminished via a single or repeated CPC procedure, lessening their risk of local or systemic adverse effects, and decreasing medication-related healthcare costs. Low- or no visual prognosis eyes can be safely treated at relatively low energy levels but repeat CPC should be considered early (most likely by the 3-month visit) if IOP is not controlled adequately. All the treated eyes had a very limited baseline visual acuity (between finger counting and no light perception) so conclusions cannot be drawn about the use of TSCPC in eyes with good visual potential in our patient population.

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