BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X.

Online ISSN 2357-0016

Preliminary Results of Micropulse Laser Transscleral Cyclophotocoagulation in Neovascular Versus Primary Open Angle Glaucoma Patients Using Zig Zag Technique

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Received:17 December 2023

Accepted:1 January 2025

Abstract:

Purpose: To compare the clinical outcome of Micro-Pulse Laser Transscleral Cyclophotocoagulation (MP-TSCPC) in neovascular glaucoma (NVG) versus primary open angle glaucoma (POAG) using Zig Zag technique.**Methods:** prospective comparative clinical study. **Participants:** 11 eyes of 10 consecutive patients with advanced NVG, and 13 eyes of 10 consecutive patients with advanced POAG in which IOP was uncontrolled despite maximum tolerated antiglaucoma medications. Treatment success: indicated by a decrease in IOP with 30%, or IOP ranging between 6 & 21 mmHg. **Results:** thirteen eyes of 10 patients with POAG and 11 eyes from 10 NVG patients were included. Postoperatively, the mean IOP in all patients significantly decreased at all follow-up points ($P<0.001$). No significant complications were noted in either group apart from 1 case of decreased VA by 1 line in POAG group. The use of ocular hypotensive medications showed significant decrease in both groups with no statistical significance on comparing between them. The success rate in POAG patients was 84.6% versus 90.9% in NVG patients at 6 months with no statistical significance between both groups ($P=1$). **Conclusion:** MP-TSCPC with ZigZag mode of application is an effective treatment for patients with NVG as POAG.

Key Words: cyclophotocoagulation, laser, refractory glaucoma, neovascular glaucoma.

Introduction

Glaucoma is the second leading cause of irreversible blindness worldwide after diabetes mellitus.[1,2] Cataract was the main reason of blindness among individuals aged fifty years as well as older on a global scale in 2020, accounting for 15.2 million cases; glaucoma accompanied with 3.6 million cases.[3]

Intraocular pressure (IOP) elevation is the sole threat that can be modified for progression of glaucomatous optic neuropathy. Decreasing IOP typically aims to be targeted initially through applying ocular hypotensive medications, surgical intervention which may be penetrating as trabeculectomy and device implantation, or non-penetrating as deep sclerectomy. For decades the use of lasers for glaucoma management was rendered as last choice either for limited effect as argon laser trabeculoplasty or selective laser trabeculoplasty which are used mainly for pigmentary glaucoma with short term effect, or for high risk for drastic complications (as retinal detachment or phthisis) as Diode laser cyclophotocoagulation (CPC).[4]

As the use of conventional diode CPC (810 nm) was deferred for the high risk of drastic complications; that is why its use was limited for blind painful eyes.[5] This idea is now changed with the evolution of micro-pulsed technology. The idea of micro-pulsed laser is to fractionate the laser power into small waves with on active cycle (variable percentage) followed by (off) inactive cycle[6,7] giving time for ablated tissue to cool down so as to prevent collateral tissue damage.[8]

Since its initial exploration in the year 1997 as a potential substitute for traditional retinal photocoagulation, the micro-pulse laser technique has proven to be efficacious in managing diabetic macular oedema while preserving functional retinal tissue, in contrast to conventional laser approaches.[9]

Preliminary results for micro-pulse diode laser in ciliary body ablation (MP-TSCPC) were very promising with high success rates and limited complications compared to conventional diode laser ablation.[8] Many studies were published reporting the outcomes of different techniques and parameters for MP-TSCPC which usually varied in period of applying laser & sequence of probing movement where the variation of used power is limited (2000 mw-2200 mw rarely reaching 2500 mw).[8,10,11–13] The variation in parameters between surgeons attempts to achieve an equilibrium among a high rate of success & low complication rate.[10]

It is well recognised that neovascular glaucoma (NVG) represents an aggressive type of glaucoma which is difficult to be managed either medically or surgically with high risk of failure.[14] Consequently, diode laser CPC is usually used for advanced cases of NVG with good success rates.[15–17] Many studies reported the outcomes of MP-TSCPC in NVG which initially was not promising[18], however, with modification of parameters and techniques further studies reported better outcomes with promising results[19–21].

This study aims at applying the Zig Zag technique to compare the outcome of MP-TSCPC in primary open angle glaucoma (POAG) to that of NVG.

Patients and Methods:

Type of study: Comparative prospective clinical intervention.

Participants: Eleven eyes from 10 consecutive patients suffering from advanced NVG as well as thirteen eyes from ten consecutive cases with advanced POAG. All patients suffered from uncontrolled IOP despite maximal tolerated antiglaucoma medications. Patients who underwent MP-TSCPC with the ZigZag technique at Mahmoud's Ophthalmic Charity Centre between March and April 2021 were enrolled in this study. After such technique, they were followed for a minimum of six months. Priority was given to recruits on a first-

come, first-served basis to include the required sample size.

Inclusion criteria: Adult glaucomatous cases with NVG or open angle glaucoma, were subjected to MP-TSCPC with the ZigZag mode because of the ineffectiveness of greatest tolerated anti-glaucoma medical therapy.

Exclusion criteria: Subjects suffering from alternative forms of glaucoma.

At the time of presentation, comprehensive medical histories were obtained from every patient, encompassing systemic disease history, personal history, previous ocular surgeries or traumas, familial predisposition to glaucoma, current illness details (including course, onset, causes of progression, duration, & current medication), & family history of glaucoma.

Ophthalmic evaluations comprised assessment of best corrected visual acuity (BCVA), gonioscopy, anterior & posterior segments exam, as well as IOP measurement.

Visual acuity was categorised into 6 classes (table 1).

Table 1: Categories of Visual Acuity

Snellen Visual Acuity	VA (LogMAR)	Category	Classification
≥ 6/18	0.0 – 0.50	0	Mild to no VI
< 6/18 – 6/60	0.52 – 1.0	1	Moderate VI
< 6/60 – 3/60 (6/ 120)	1.0 – 1.30	2	Sever VI
< 3/60 – 1/60	1.32 – 1.80	3	Blindness
< 1/60 – LP	1.82 – 3.0	4	Blindness
NLP	4.0	5	Blindness

Note: Low vision refers to visual impairments that range from moderate to severe.
visual acuity, VA; LogMAR, logarithm of minimum angle of resolution; VI, LP, visual impairment; NLP, perception of light; no perception of light.

Cases were investigated with central corneal thickness measurement, Optical coherence tomography (OCT) of the optic nerve head, visual fields testing, as well as ocular ultrasonography were employed with difficult fundus examination to identify pathology as well as document the state of the retina.

All the information was recorded to compare it with post-operative outcomes, including number of medications, IOP reduction, as well as complications.

Ethical consideration:

All procedures were performed according to the relevant guidelines and regulations of the ethical committee of Helwan University (serial: 14-2021).

Written informed assent was obtained from every person involved in the research subsequent to providing them with pertinent information regarding the study.

Protecting the confidentiality of participants through:

The information was restricted to the research team exclusively.

Surgical procedure:

Laser was applied by the same technique (MP-TSCPC), same surgeon (T.A.), under peri-bulbar anaesthesia, either with or without systemic sedation. Gel lubricant was utilized to aid probe movement. Utilizing an MP3 handpiece (IRIDEX, CYCLO G6 Glaucoma Laser System, Mountain View, CA) equipped with fixed laser settings (2000-mW of 810-nm infrared diode laser in micro-pulse delivery mode with a 31.3 percent duty cycle, with an on-cycle of 0.5 milliseconds then an off-cycle of one milliseconds), the technique was performed. ZigZag laser delivery will be utilized in relation to the anatomical structure of the body of cilia. The CPC probe is moved within two millimetres, in a zigzag fashion,

perpendicular to a line 3 millimetres away from the limbus, to treat the largest area of ciliary body circumference. Laser is applied over three quadrants for duration of ninety seconds per quadrant (a total of two hundred seventy seconds). This spares the fourth quadrant, which has not been utilized, for additional intervention.

Treatment success: IOP within the range of six to twenty-one millimetres of mercury or a decrease of thirty percent in IOP. A further classification for achievement was qualified success, in which antiglaucoma medications were required after MP-TSCPC to achieve the target IOP, or complete success, in which no post-operative antiglaucoma medications were required to achieve the target IOP. Non-success was defined as failure to satisfy the requirements for achievement or the necessity to retreat.

Follow up visits: At one week, one month, three months, as well as six months after treatment reported, BCVA, the number of post-operative medications, the IOP was evaluated based on sustainability of results, and the percentage of reduction and as well as complications that were reported.

Statistical Analysis: Sex, Age, laterality as well as side, diabetes status, glaucoma interventions, prior operations or central corneal thickness, IOP before & after the procedure, intraoperative as well as one week, three, six postoperative complications, classification of preoperative visual acuity, as well as the number of medications administered prior to & at monitoring visits were all recorded for every patient.

Results

Data was analysed using the statistical package for social science (SPSS), 25th version.

Description: 24 eyes of 20 patients were included in the present study, which were classified into 2 groups; group (A) for POAG patients, and group (B) for NVG patients. From March to April 2021, MP-TSCPC was administered to manage those patients. The minimum monitoring period was six months, throughout which the initial findings of the methodology were computed by calculating data at one-week, one-month, three-month, as well as six-month intervals. Regarding Group A, (POAG) There were 4 males (30.8%) and 9 females (69.2%). The median age of patients was 53.2 (± 1.7) years old. Right eye of 6 patients (46.2%) and left eye of 7 (53.8%) underwent treatment with MP-TSCPC. On the other hand, Group B (NVG) showed 5 males (45.5%) and 6 females (54.5%) with mean age of 60 years (IQR: 51-64). The right eye was treated in 2 cases while the left eye was treated in 9 cases. Moreover, 10 cases were bilaterally glaucomatous in group A (76.9%), while only 4 cases in group B (36.4%).

Previous ocular interventions: In group (A) 3 cases (23.1%); a history of cataract extraction as well as IOL implantation was disclosed, and only one case reported history of LASIK surgery. In Group (B) 7 cases (63.6%), a history of cataract extraction as well as IOL implantation was disclosed, 3 cases (27.3%) reported pars plana vitrectomy,and intravitreal medication injection in 4 cases (36.4%). Regarding previous glaucoma interventions, group (A) showed 1case (7.7%) with reported history of sub-scleral trabeculectomy, while group (B) showed 1case (9.1%) with reported history of Ahmed valve placement, 1case (9.1%) with history of sub-scleral trabeculectomy, and 1 case (9.1%) with history of conventional diode CPC.

Preoperative visual acuity: In group (A): 2 eyes (15.4%) were categorized as class one, 5eyes (38.5%) were categorized as class three, and 6 eyes (46.5%) were classified as category 4. Regarding group (B): 2 cases (18.2 %) were classified as category 1, 4 cases (36.4%) were classified as category 3, while 5 cases (45.5%) were classified as category 4.

Medications: We classified the perioperative medications into three categories; class one: topical carbonic anhydrase inhibitors (CAI) + beta blockers, that had been recommended for 1case (7.7%) in group A and 1case (9.1%) in group (B). Class two: topical CAI + beta blockers + alpha agonists +/or prostaglandin analogues was prescribed for 6 cases (46.2%) of group (A), and 5 cases (45.5%) in group (B). Class 3: any topical antiglaucoma medications + systemic CAI which was prescribed for 6 cases (46.2%) in group (A) and 5 cases (45.5%) in group (B). MP-CPC was directed for noncompliance or non-effectiveness of treatment in first 2 classes. Freidman test was used to determine statistical-significant change in number of medications before and after laser technique in each of the groups (table 2, figure1). There was no statistically significant difference in number of medications among the POAG patients (p-value = 0.149), while there was a statistically significant decrease in number of medications among NVG patients (p-value = 0.021).

IOP reduction: Freidman's test showed statistically significant change in IOP before and after the diode laser (p-value < 0.001). There was statistically significant decrease in IOP in the 4 follow-up visits in both groups (table 3).

Difference in IOP reduction between both groups: The IOP reduction among the two groups was compared using the Mann-Whitney U test for non-normally distributed information & the student's t-test for data that is normally distributed. No statistically significant difference between both groups in percentage reduction of IOP among the 4 follow-up visits (figure2).

Success rate: Chi^2-test and Fisher's Exact test were used to compare success rate between POAG and NVG. However, no statistical difference was found (table 4)

Table 2 Number of medications in both groups (data presented as median, IQR)

Timing	**POAG**		**NVG**	
	Number of medications	p-value	Number of medications	p-value
Preoperative	4 (3,4.5)		3 (3,4)	
1st week	3 (3,3)	0.033	3 (3,3)	0.16
1st month	3 (3,3)	0.046	3 (0,3)	0.02
3rd month	3 (2,3)	0.018	2 (0,3)	**0.005**
6th month	3 (2,3)	**0.007**	2 (0,3)	**0.003**

Table 3 compares preoperative IOP to post-operative IOP in each visit in both groups

	POAG	**NVG**
pre-operative vs 1st week	**0.00146**	**0.00330**
pre-operative vs 1st month	**0.00236**	0.00503
pre-operative vs 3rd month	0.00185	**0.00331**
pre-operative vs 6th month	0.00147	**0.00506**

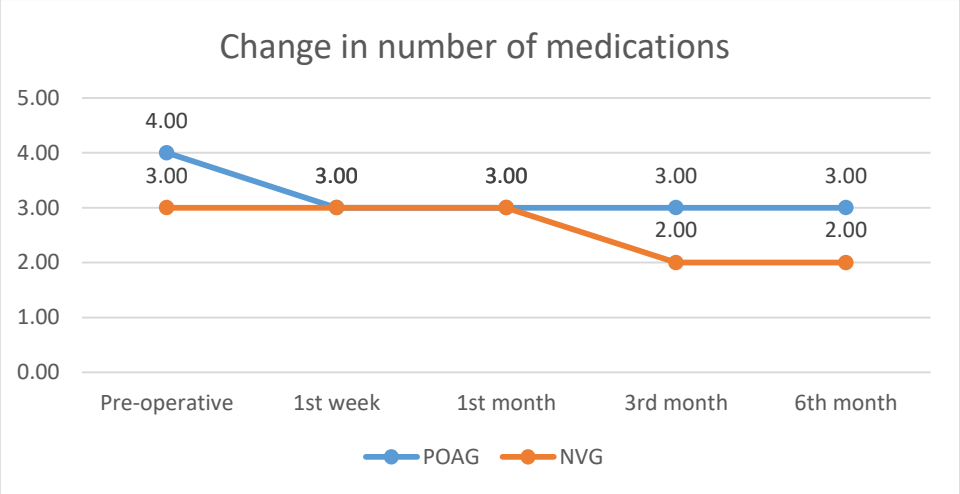

Figure 1 Change in number of medications in POAG and NVG groups

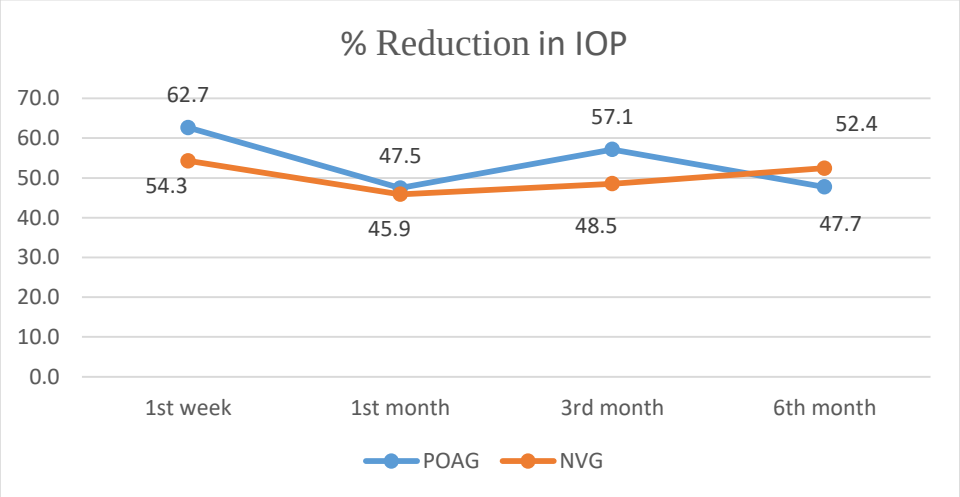

Figure 2 Percentage reduction in IOP in both groups

Table 4 Success rate among POAG (N=13) and NVG (N=11)

	Diagnosis		p-value	OR (95% CI)
	POAG	NVG		
1st week	13 (100%)	11 (100%)	-----	-----
1st month	13 (100%)	11 (100%)	-----	-----
3rd month	12 (92.3%)	9 (81.8%)	0.58	0.38 (0.03-4.8)
6th month	11 (84.6%)	10 (90.9%)	1	1.8 (0.14-23.3)

Discussion:

MP-TSCPC, as a recent technique for treating refractory glaucoma has a significantly lower incidence of complications than conventional diode. Different parameters & patterns of application are being described with no fixed recommendations for all cases.[8] Diverse studies implemented methods of therapy that varied in terms of power, application time, as well as probing movement pattern throughout application, resulting in varying rates of success as well as complications.[12,13,22]

It is now understood that the rate of complications increases in direct

proportion to the focal application power & time.[8] It is also well known that NVG is one of the most aggressive types of glaucoma with limited successful ways of management.[13]

MP-CPC was described for management of refractory glaucoma with promising success rates in POAG, however its results in neovascular and pediatric glaucoma is still debatable.[8,12,19–21]

In the current study, it was decided to compare the outcome of Application of micro-pulse diode laser CPC with zigzag pattern in neovascular glaucoma to that of POAG. The surgeon used the ZigZag technique for probe movement with fixed power of 2000mj, active duration cycle of 0.5ms (31.3%) on-mode to decrease the focal energy per application point thus reaching the widest area of ciliary processes with least collateral damage. This would consequently decrease the rate of complications with maximum ciliary body photocoagulation and IOP reduction which was achieved within two hundred seventy seconds, that is a comparatively a prolonged application period. [6,22,24–26]

Success rate: The present research defined achievement as an intraocular pressure (IOP) reduction of thirty percent or greater from preoperative IOP, regardless of the use of topical antiglaucoma medications. This was achieved in 11 cases (84.6%) at final follow up (after 6 month) in group (A) and in 10 (90.9%) cases in group (B) at final follow up with no statistical significance between both groups {p =1 OR :1.8 (0.14-23.3)}. The success rate of both groups was higher than reported by Alice Williams et al[13] who documented a sixty-seven percent rate of achievement at the three-month monitoring in their retrospective study. In addition, Zaarour & colleagues [23] documented a comparatively lower rate of success, but this was limited to white subjects. In contrast, the present study exclusively comprises African descendants as patients, a demographic known for its more aggressive form of glaucoma in addition to the aggressive nature of neovascular glaucoma in group (B). Also Tan and their colleagues reported lower success rate is neovascular group where they included 12 cases with success rate 50%.[18] Magacho & colleagues additionally documented a reduced achievement rate of 86.5 percent regardless of employing an extended period of three hundred & twenty seconds distributed across two distinct sessions, they also included 3 cases of neovascular glaucoma in which 2 cases reported prolonged hypotony.[12] Yelenskiy and colleagues also reported lower success rates (71%), that might be associated with achieving the criteria stated (post-operative intraocular pressure of less than eighteen millimeter of mercury).[19] In contrast, Al Habash & their colleagues in 2019 conducted a prospective investigation encompassing seventy-one eyes & reported a significantly greater achievement rate of ninety-five percent Among these eyes, twenty-four cases of neovascular glaucoma were incorporated, contributing to an overall rate of success of 91.7 percent. [20] This might be attributable to the relatively higher power (2200mw) utilized in the present investigation.

Intraocular pressure reduction: In group (A) of POAG, ZigZag technique achieved 47.7% reduction of preoperative IOP (median 40 mmHg, (IQR: 30.5 - 41 mmHg)) as related to postoperative IOP (median 18mmHg) at six-month of monitoring, while in group (B) also significant reduction of IOP was achieved (52.4%) where the preoperative median IOP was 40mmHg (IQR: 26 - 50 mmHg) and the post-operative IOP was found to be 18mmHg (IQR: 12 - 20mmHg). This IOP decrease in the two groups is greater than that reported in the study by Emanuel et al., despite the relatively prolonged laser application duration. As with extended laser application times, however, it was observed a greater reduction in intraocular pressure. [10]

Number of medications: Additionally,

the administration of ocular hypotensive medications declined significantly in group (B) where the median number of medications decreased from 3 drugs (IQR: 3 – 4 drugs) to 2 drugs (IQR: 0 – 3 drugs) with 40% reduction, while in group (A) the number of medications decreased from 4 drugs (IQR: 3 - 4.5 drugs) to 3 drugs (IQR: 2 – 3 drugs) (33.3% reduction) in last follow up. On comparing the percentage of reduction between both groups there was no statistical significance. This value surpasses the figures documented by Niten Vig & colleagues (17.8 percent) as well as Emanuel & colleagues (41.2 percent).[26,10] Conversely, Toyos et al. demonstrated a greater reduction (45.5 percent) in the medications number used at the end of following period.[27]

Rate of complications: MP-TSCPC is currently favoured over conventional CPC due to its minimal complication rate as well as safety.[24] The authors of the present investigation did not observe any complications in neovascular glaucoma group (group B), while in group (A), A mere one case (7.7%) presented with a reduction in visual acuity of one line. When compared to neovascular group in the Magacho study, who reported 2 cases of prolonged hypotony (67%) in neovascular glaucoma patients (n=3), however no complications was reported in the other glaucoma types.[12] This might be attributed to the ZigZag patterning, which reduces collateral tissue injury as well as focal ablation. When comparing the findings to those of Emanuel et al., who used a comparable application time, they discovered five instances of protracted hypotony and twenty-eight cases (forty-six percent) of long-term inflammation (after three-month of treatment).[10] Additionally, seven complex cases (8.8 percent) were reported by Alice Williams as well as her colleagues using their innovative probe movement (stop and go) technique.[13] FG Sanchez et al., Ahmed Al Habash et al., and Yelenskiy et al. all reported the absence of complications.[25,20,19]

Limitations This study has a limited sample size and this necessitates its application to a larger population in order to obtain more dependable outcomes. Furthermore, the objective of evaluating the effectiveness of this novel technique in a solitary session hindered the execution of supplementary sessions on cases that failed, to ascertain its repeatability with respect to decrease in IOP and incidence of complications. Additionally, an extended follow-up period is necessary to identify long-term effects.

Conclusions:

MP-TSCPC with ZigZag method of implementation is an effective management for instances with neovascular glaucoma with similar results to primary open angle glaucoma. Increased success rates as well as decreased occurrence of complications despite the extended duration of application support the idea of Zig Zag technique as an effective technique to cover the widest portion of ciliary processes with minimal focal burn which gives promising way for management of neovascular glaucoma.

Funding declaration: Aside from grants, funds, & other forms of assistance, the authors affirm that none were obtained in the course of preparing this manuscript.

Competing interest: There are no pertinent financial or non-financial interests to disclose through the authors.

Author Contribution: All authors made contributions to the conception & design of the investigation. The researchers conducted gathering information, material preparation & analysis {Tarek T. AboulNasr, Ahmed S. Abo-Hussein, and Ahmed F. El-Shahed}. The first draft of the manuscript was written through [Ahmed S. Abo-Hussein] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration for data availability: The

datasets utilized as well as analyzed in the present study are available upon an appropriate request from the corresponding author.

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To cite this article: Ahmed S. Abohussein, Tarek T. Aboulnasr, Ahmed F. El-Shahed. Preliminary Results of Micropulse Laser Transscleral Cyclophotocoagulation in Neovascular Versus Primary Open Angle Glaucoma Patients Using Zig Zag Technique. BMFJ 2025;42(3):204-213.