DOI:10.14744/bej.2024.47123
Beyoglu Eye J 2024; 9(1): 1-7

Systematic Review

A Systematic Review of Cyclophotocoagulation Techniques: Continuous Wave Versus Micropulse for Glaucoma Treatment

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Abstract

Objectives: Micro-pulse cyclophotocoagulation (MP-CPC) represents the latest iteration of minimally invasive laser procedures aimed at reducing intraocular pressure (IOP) through the disruption of pigmented ciliary body epithelium. This systematic review aims to assess the efficacy and safety profile of the MP-CPC procedure in comparison to CW-CPC for the treatment of glaucoma.

Methods: We initiated a search on PubMed, ScienceDirect, and the Cochrane Library databases for studies that compared micro-pulse and traditional CW-CPC in terms of their efficacy and safety profiles. We employed medical subject headings terms and keywords such as "cyclophotocoagulation," "cyclodestructive," "photocoagulation," "CPC," "micropulse," "micro-pulse," and "glaucoma" within the timeframe from 2015 to 2023. We assessed the success rate, IOP reduction, antiglaucoma medications, and complications of MP-CPC and CW-CPC.

Results: We included six articles in this study, comprising two randomized controlled trials, three retrospective, and one prospective cohort, published between 2015 and 2023. Five out of six reported a significant reduction in IOP for both procedures with comparable success rates observed in MP-CPC compared to CW-CPC. One article reported an increase in IOP in MP-CPC. Both groups reported a decrease in the number of antiglaucoma medications, while one study reported an increase in medications in both MP-CPC and CW-CPC groups. Complication rates were lower in the MP-CPC group with two articles reporting a significant decrease compared to the CW-CPC group.

Conclusion: MP-CPC has shown promising results in the treatment of glaucoma in the adult population. With comparable results in IOP reduction and fewer instances of serious ocular complications, MP-CPC may open new possibilities for the use of cyclophotocoagulation procedures in the earlier stages of glaucoma. However, its efficacy in the pediatric population and for neovascular glaucoma remains less defined, thus warranting further studies to establish optimal laser parameters for different types of glaucoma and specific populations of glaucoma patients.

Keywords: Cyclophotocoagulation, glaucoma, micro-pulse.

Introduction

Glaucoma, a group of optic neuropathies, is the leading cause of irreversible blindness worldwide. An estimated 80 million people are currently impacted, with this number projected to rise to 111.8 million by 2040 (1). The gradual deterioration of the optic nerve leads to peripheral vision impairment, a progression that often remains undetected until the disease is advanced. As such, recognizing and managing glaucoma at an early stage is vital to prevent vision loss (2).

How to cite this article: Johansyah CAP, Bambang L. A Systematic Review of Cyclophotocoagulation Techniques: Continuous Wave Versus Micropulse for Glaucoma Treatment. Beyoglu Eye J 2024; 9(1): 1-7.

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Submitted Date: September 04, 2023 **Revised Date:** December 31, 2023 **Accepted Date:** January 05, 2024 **Available Online Date:** March 01, 2024

Beyoglu Eye Training and Research Hospital - Available online at www.beyoglueye.com

Given the close connection between glaucoma progression and elevated intraocular pressure (IOP), the primary focus of most interventions is to lower the IOP. Various approaches, including the use of topical or oral medications, laser procedures, and surgical interventions, can be chosen based on the specific type and severity of glaucoma (3). Cyclophotocoagulation is an invasive strategy for treating glaucoma, employing lasers to disrupt underlying pigmented ciliary body epithelium and vascular core of the ciliary body, thereby reducing aqueous humor production. Due to the risk of serious complications such as inflammation, chronic hypotony, and phthisis bulbi, this therapeutic method is kept for cases where traditional surgical approaches have failed, are unsuitable, or for individuals with refractory glaucoma (4,5).

Micro-pulse cyclophotocoagulation (MP-CPC) is the latest minimally invasive laser procedure in which the laser is emitted in repetitive pulses, interspersed with rest periods, allowing a gradual accumulation of heat energy in the targeted cells. In contrast to traditional continuous wave laser treatments (CW-CPC), the micro-pulse approach permits thermal relaxation, resulting in less extensive tissue disruption in the ciliary processes, epithelium, and adjacent non-melanin-producing tissue. This, theoretically, leads to fewer post-treatment complications as mentioned earlier (6,7).

Due to the relatively early stage of this procedure, comparisons between micropulse and CW-CPC are uncommon. This study aims to compare the efficacy and safety of both procedures in terms of IOP reduction, additional medication usage, and post-treatment complications.

Methods

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, and its process was documented using a PRISMA flow diagram, as shown in Figure 1 (8,9). The limited number of randomized controlled trials (RCTs) was evident from a prior review, prompting the inclusion of RCTs, case series, and retrospective cohorts in this study (10).

Search Strategy

We initiated a search on PubMed, ScienceDirect, and the Cochrane Library databases for studies that compare micropulse and traditional CW-CPC in terms of their efficacy and safety profiles. We employed Medical Subject Headings terms and keywords such as "cyclophotocoagulation," "cyclodestructive," "photocoagulation," "CPC," "micropulse," "micro-pulse,' and 'Glaucoma' within the timeframe from 2015 (when FDA approved micro-pulse laser use in cyclophotocoagulation for glaucoma) to 2023. The final search was conducted in late August 2023.

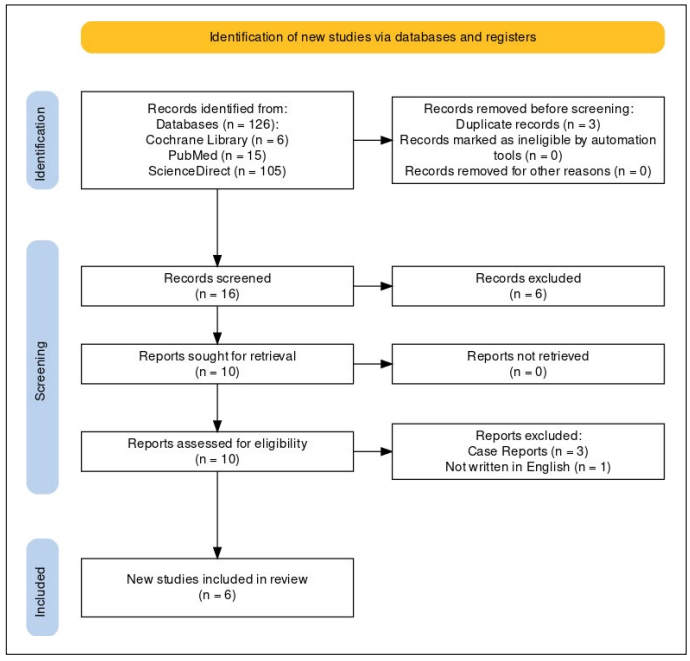

Figure 1. PRISMA flowchart.

Eligibility and Selection Criteria

Two reviewers conducted a literature search and independently screened the research articles. Included studies must meet the following criteria: (1) All study types except case reports or reviews (e.g., RCTs, retrospective or prospective cohort studies, and case series); (2) comparative studies of micro-pulse and CW-CPC procedures; (3) written in English; (4) full text is available. All types of glaucoma were included in the study. There were no restrictions on gender, age, or prior medication or surgical interventions. Duplicate publications and procedures combined with other types of surgery were excluded from the study. The reviewers extracted the necessary data, and any disagreements were resolved through discussion.

Data Extraction

Studies are graded based on the Oxford Centre for Evidence-Based Medicine level of evidence. The observed outcomes include IOP reduction, success rate, number of required medications, and complications. The primary outcomes examined were the IOP before and after the procedure, as well as the success rate. Secondary outcomes encompassed the number of medications required and post-procedure complications such as anterior chamber (AC) inflammation, phthisis bulbi, and persistent ocular hypotony.

Statistical Analysis

Given the nature of this systematic review, no statistical tools were employed. The studies included in this review utilized various tools to analyse their respective data. Aquino et al. used R version 2.14.2 (R Development Core Team,

R Foundation for Statistical Computing, Vienna, Austria) while Zemba et al. used R statistical language and "nlme" package version 3.1–148 (11,12). Abdelrahman and El Sayed performed the statistical analysis using SPSS for Windows version 15.0.1 (SPSS Inc., Chicago III, IL), Abdullatif and Ahmed El-Saied using IBM SPSS version 24 (International Business Machines Corporation (IBM), Armonk, NY, USA), and Bernardi and Töteberg-Harms using IBM SPSS version 26 (International Business Machines Corporation (IBM), Armonk, NY, USA) (4,13,14). All studies considered $p<0.05$ as statistically significant.

Results

A total of 126 articles were identified in our preliminary search. After identifying and removing three duplicates, we reviewed 15 full-text studies. Six final articles were included in this study, comprising two RCTs, three retrospective cohorts, and one prospective cohort, all published between 2015 and 2023. All six of these articles were assigned an Oxford level 2 grade, as outlined in Table 1.

Success Rate

Success definitions varied across the studies. Two studies considered successful treatment as achieving an IOP range between 6 and 21 mmHg or a reduction of >30% from the baseline. In another study, success was defined as either an IOP between 6 and 21 mmHg or an IOP reduction of >20% from baseline (11,13). In addition, one study considered treatment successful when IOP was in the range of 5–21 mmHg with no other signs of glaucoma progression (increasing corneal diameter, axial length, and cup-to-disc ratio (4). Another study defined success as achieving an IOP <21 mmHg after the procedure or achieving >30% IOP reduction from the baseline, with or without antiglaucoma medications (12). On the contrary, failure was defined as the inability to meet success criteria or in cases where devastating complications occurred, as observed in three studies (4,12,13). The need for retreatment was considered a failure in one study (14).

RCT study conducted by Aquino et al. reported a significantly higher success rate in MP-CPC (75%) compared to CW-CPC (29%) in 12-month ($p<0.001$) and 18-month post-treatment (52% vs. 30%, $p=0.03$) (11). A study by Abdullatif and Ahmed El-Saied demonstrated higher success rate in MP-CPC (60%) than CW-CPC (50%) in 6 months after treatment although it is not statistically significant ($p=0.8$) (13). Same went in prospective cohort study by Abdelrahman and El Sayed showing advantage in MP-CPC compared to CW-CPC (72% vs 54%, failure rate $p=0.1$) (4). However, retrospective studies by Bernardi and Töteberg-Harms and Zemba et al. showed a higher success rate achieved by CW-CPC compared to MP-CPC after 12 months post-treatment (88.6% vs. 87.5% and 54% vs. 33%) although these differences were not statistically significant ($p=0.883$ and $p=0.15$) (12,14).

Table 1. Study characteristics

No	Reference	Study design	Level of evidence	Intervention	Sample size (eye)	Outcome observed
1	2015, Maria Cecilia D Aquino	Randomised Controlled Trial	2	MP-CPC vs. CW-CPC	48	success rate; IOP at baseline, 1st day, 1st week, 1st, 3rd, 6th, 12th, 18th month; antiglaucoma medications; complications
2	2018, Ahmed M. Abdelrahman	Prospective Cohort	2	MP-CPC vs. CW-CPC	45	success rate; IOP at baseline, 2nd week, 1st, 3rd, 6th month; antiglaucoma medications; complications
3	2020, Anthony Fam	Retrospective Cohort	2	MP-CPC vs. CW-CPC	31	IOP at baseline, 1st, 3rd, 6th, 12th month, antiglaucoma medications, retreatments
3	2020, A. M. Abdullatif	Randomised Controlled Trial	2	HFU vs. MP-CPC vs. CW-CPC	30	success rate; IOP at baseline, 1st day, 1st, 2nd week, 1st, 2nd, 3rd, 6th month; antiglaucoma medications; complications
4	2021, Enrico Bernardi	Retrospective Cohort	2	MP-CPC vs. CW-CPC	197	success rate; IOP at baseline, 1st day, 1st week, 1st, 3rd, 6th, 9th, 12th month, antiglaucoma medications; BCVA
5	2021, Mihail Zemba	Retrospective Cohort	2	MP-CPC vs. CW-CPC	46	success rate; IOP at baseline, 1st day, 1st week, 1st, 3rd, 6th, 9th, 12th, 15th month; antiglaucoma medications, complications, BCVA, need for retreatment

MP-CPC: Micro-pulse cyclophotocoagulation; CW-CPC: continuous wave cyclophotocoagulation.

Reduction in IOP

Reductions in IOP were observed in both the MP-CPC and CW-CPC groups at the 6-month mark after treatment and at the respective studies' final follow-up assessments. Bernardi and Töteberg-Harms reported significant IOP reductions compared to baseline in both the MP-CPC (22 to 15.7 mmHg, p<0.001) and CW-CPC groups (28.3 to 15.3 mmHg, p=0.005) after 12 months, with a similar result in both groups (p=0.815) (14). Similarly, a study by Zemba et al. demonstrated comparable findings, displaying statistically significant IOP reduction from baseline in both groups (34.71 to 26.67 mmHg in MP-CPC and 35.82 to 23.86 mmHg in CW-CPC, p<0.05), and similar IOP levels in both groups after 12 months (p=0.49) (12). Consistent outcomes were evident in studies by Aquino et al. (36.5 to 20 mmHg in MP-CPC and 35 to 19 mmHg in CW-CPC), Abdelrahman and El Sayed (28.3 to 16.4 mmHg in MP-CPC and 27.5 to 17.9 mmHg in CW-CPC), and Abdullatif and Ahmed El-Saied (18.7 to 15.4 mmHg in MP-CPC and 19.8 to 14.4 mmHg in CW-CPC), wherein the differences in IOP between MP-CPC and CW-CPC were not statistically significant at the final follow-up of each study (p=0.70, p=0.30, p=0.30). Notably, these studies did not provide information regarding the statistical significance of the final IOP in comparison to the baseline (4,11,13). Nonetheless, a study conducted by Fam et al. indicated that IOP reduction was observed only in the CW-CPC group, whereas the MP-CPC group experienced an elevation in IOP after 12 months of follow-up. CW-CPC group demonstrated a decrease in IOP from 38.9 to 26.5 mmHg, while the MP-CPC group noted an increase in IOP from 31.6 to 34 mmHg. This discrepancy between the two groups held statistical significance (p<0.001) (15).

Number of Antiglaucoma Medication

Five out of six studies reported a decrease in the number of medications required to manage IOP following both MP-CPC and CW-CPC treatments. A similar number of medications were found to be necessary for MP-CPC and CW-CPC, with slightly fewer medications required for CW-CPC in those studies. Abdullatif and Ahmed El-Saied study indicated a reduction in medications from 4 to 3 and 2.5, respectively, for MP-CPC and CW-CPC (p=0.04). Similarly, Bernardi and Töteberg-Harms presented comparable results, demonstrating reduced medication usage in both treatment groups. However, it was in the CW-CPC group where medication reduction was statistically significant (33%, p<0.001, compared to 7.14%, p=0.551 in the MP-CPC group). The discrepancy between them at the final follow-up was nearly equal (p=0.06). Aquino et al., Abdelrahman and , and Zemba et al. reported similar findings, with the MP-CPC treatment group requiring slightly more or a similar number of medications to manage IOP, although no statistical significance was mentioned. On the contrary, a study by Kawaji et al. observed an increase in the number of medications required in both the MP-CPC and CW-CPC groups, with the count rising from 1.70 to 2.00 in the MP-CPC group and from 1.56 to 1.61 in the CW-CPC group. The difference between these two groups remained statistically insignificant (p=1.00) (16).

Complications

Four out of six studies reported the rate of complications for both MP-CPC and CW-CPC, with MP-CPC showing superior outcomes. In a study by Aquino et al., only 12% of MP-CPC cases experienced ocular complications, including prolonged AC inflammation, scleral thinning, and declining visual acuity. In contrast, the CW-CPC group exhibited a complication rate of 60%, with one case resulting in phthisis bulbi (p=0.01). Another study by Zemba et al. showed greater number of complications in CW-CPC group compared to MP-CPC (p=0.045) with two cases of phthisis bulbi in CW-CPC treatment group. Abdelrahman and El Sayed reported similar result, with the only complication happened in MP-CPC treatment group was ocular hypotony, which was resolved with conservative treatment and considered complete success 6-month post-treatment. Three cases of hypotony were reported in CW-CPC treatment group, two of them resolved, and one developed phthisis bulbi. In addition, two cases of anterior uveitis were reported in CW-CPC treatment group. However, the difference of complication rate in both groups was not statistically significant (p=0.30). Abdullatif and Ahmed El-Saied reported four instances of post-operative complications within the CW-CPC group, wherein one eye developed phthisis bulbi, while the other three experienced severe pain and anterior uveitis. In contrast, only one eye in the MP-CPC group developed uveitis. Despite the presence of more severe complications in the CW-CPC group, the difference between the MP-CPC and CW-CPC groups was not statistically significant (13). Although the report by Fam et al. did not mention the complication rate, 46% of patients (six eyes out of 13) required retreatment in the MP-CPC group, compared to 28% (five eyes out of 18) in the CW-CPC group (15). A different result was observed by Zemba et al., where fewer patients in the MP-CPC group (6 eyes out of 24/25%) required retreatment compared to the CW-CPC group (7 eyes out of 22/32%), albeit without mentioning statistical significance (12).

Discussion

MP-CPC represents the latest iteration of CW-CPC, CP-CPC, utilizing a pulsatile laser energy approach. It involves alternating between delivering short bursts of energy (ranging from 1600 mW to 2500 mW of 810 nm laser for 0.5 ms) and subsequent resting periods (1.1 ms). This technique effectively targets the pigmented epithelium of the ciliary body,

while safeguarding surrounding tissues from thermal damage to mitigate ocular complications. The destruction of the pigmented epithelium and impairment of the ciliary body's vascular supply result in reduced aqueous humor production, consequently lowering IOP. In addition, the inflammation triggered by this process enhances uveoscleral outflow through the release of prostaglandins, further contributing to IOP reduction (7,17,18).

Aquino et al. published the first RCT in 2015, comparing MP-CPC and CW-CPC in refractory glaucoma patients, with a follow-up duration of up to 18 months post-treatment. The study included glaucoma patients aged 21 or older, who had not responded to maximal tolerated medical therapy with or without prior surgical intervention, were unsuitable candidates for filtration therapy, and had poor visual function. The success rate at final follow-up (IOP between 6 and 21 mmHg and reduction of IOP >30%, with or without medications), frequency of repeated treatments or medications, and complications were recorded. This study reported comparable efficacy of both MP-CPC and CW-CPC in lowering IOP, sustained for 18 months, with similar rates of retreatment in both groups. However, MP-CPC demonstrated a more predictable and consistent effect on IOP and a lower incidence of vision-threatening complications, resulting in fewer treatment failures after 18 months compared to CW-CPC. The results supported the hypothesis that the pulsatile nature of laser application in MP-CPC leads to fewer ocular complications by minimizing thermal damage to surrounding tissue while maintaining similar efficacy to traditional CW-CPC. Nevertheless, the study had limitations, including the absence of a standardized treatment protocol due to insufficient data on optimal treatment settings, inadequate stratification of glaucoma diagnoses, and intrinsic endpoints used in CW-CPC, leading to less predictable and consistent effects on IOP (11).

Another randomized controlled study conducted by Abdullatif and Ahmed El-Saied in 2020 compared three modes of cyclophotocoagulation treatments (high-intensity focused ultrasound (HIFU) cyclophotocoagulation, MP-CPC, and CW-CPC for the treatment of non-refractory glaucoma. Non-refractory glaucoma was defined as patients with no history of previous laser or surgical interventions. The study included patients with open-angle glaucoma who were medically uncontrolled, had good visual function, and were 21 years or older. Significant reductions in IOP were observed in all groups at all post-operative follow-ups, with CW-CPC achieving the greatest reduction in IOP (31.5%), followed by MP-CPC (23.9%) and HIFU (19.4%) after 6 months. The success rates at the final follow-up were 50%, 60%, and 50% for CW-CPC, MP-CPC, and HIFU, respectively, with no significant differences among these groups. The authors mentioned that variations in study populations and the absence of repeated cyclophotocoagulation sessions in this study may have contributed to slightly lower IOP reduction and success rates compared to other studies. Reductions in the number of medications and the discontinuation of oral Acetazolamide were observed in all groups, with the CW-CPC group showing the greatest reduction in the use of antiglaucoma medications. This study reported a higher complication rate in the CW-CPC group compared to the HIFU and MP-CPC groups, with HIFU not encountering complications apart from pupil distortion. However, the differences between these groups were not statistically significant (13).

A prospective study by Abdelrahman and El Sayed in 2018 compared the efficacy and safety profile of MP-CPC and CW-CPC in refractory pediatric glaucoma patients. Subjects were children under 12 years of age with uncontrolled glaucoma who required cyclophotocoagulation in September 2016 to August 2017 at Abureish Children's Hospital, Cairo University with follow-up period of 6 months. The success rate of the MP-CPC group was higher than that of the CW-CPC group, although the difference was not statistically significant. The study notes that the success rates for both MP-CPC and CW-CPC were expected to decline over time due to the ciliary body's higher regenerative ability in children and the positional variability of the ciliary body in buphthalmic eyes, which hindered accurate laser beam localization (19,20). Nonetheless, the success rate of MP-CPC in this study remained superior to what had been previously reported for CW-CPC in the pediatric group. Patients treated with MP-CPC exhibited fewer ocular complications compared to the CW-CPC group, consistent with prior reports for both adults and pediatric cases. Post-operative pain was exclusive to the CW-CPC group (14%), with no complaints of pain following MP-CPC procedures. Prolonged inflammation was more prevalent in the CW-CPC group (30%) than the MP-CPC group (4%). Abdelrahman and El Sayed mentioned that a significantly higher number of eyes in the MP-CPC group had previously undergone CW-CPC compared to the CW-CPC group. This discrepancy might influence the results of MP-CPC since these eyes were potentially more resistant to cyclophotocoagulation or had greater regenerative ability. Limitations of the study included an inability to grade and compare the anterior uveitis rates of both groups, a short follow-up period, a small sample size, and the use of a Perkins tonometer (4).

Fam et al. conducted a retrospective cohort study in 2020 involving subjects with refractory pediatric glaucoma aged 18 years or younger, comparing the use of MP-CPC and CW-CPC. This study reported that the CW-CPC group achieved a significant decrease in IOP after 12 months of follow-up, while the MP-CPC group recorded an increase in

IOP. The number of re-treatments required was also higher in the MP-CPC group compared to the CW-CPC group. However, both groups experienced an increase in the number of antiglaucoma medications needed after the final follow-up. The authors mentioned that the laser parameters used in the MP-CPC group might not have been optimal for pediatric patients with refractory glaucoma, potentially affecting the suboptimal outcomes observed in this study (15).

Bernardi and Töteberg-Harms published a retrospective cohort study in 2021 comparing the efficacy and safety profiles of MP-CPC and CW-CPC in various types of glaucoma treated between 2016 and 2020 in Zurich, Switzerland. Patients with primary and secondary glaucoma at moderate to advanced stages were included in this study. MP-CPC was found to have similar efficacy compared to CW-CPC after 12 months of follow-up, with both procedures resulting in significant reductions in IOP and the number of medications used. The success rates of MP-CPC and CW-CPC were 87.5% and 88.6%, respectively, with no statistically significant difference between the two groups. The study mentioned that the success rates of MP-CPC and CW-CPC were slightly higher than those reported in other studies, possibly due to the non-refractory nature of glaucoma and lower baseline IOP in the study population (14).

The latest study comparing MP-CPC and CW-CPC was a retrospective cohort study conducted by Zemba et al. in 2021. The subjects were patients with neovascular glaucoma (NVG) who underwent transscleral cyclophotocoagulation (TSCPC), with a final follow-up at 15 months. Cycloablative procedures like TSCPC are commonly chosen for NVG treatment due to their incision-free nature, ease of performance, short learning curve, compatibility with anticoagulants, rapid onset of effects, and repeatability. MP-CPC was found to be effective in the short term, with a high success rate initially, but this success declined over time (70.8% at the 1st week to 29.1% at 12 months). In comparison to other studies, the success rate of MP-CPC in this study was lower, which could be attributed to the specific inclusion of advanced NVG cases known for having poorer outcomes and suboptimal laser settings leading to inadequate long-term IOP control. On the other hand, CW-CPC exhibited more consistent IOP control during follow-ups, in line with the results of other studies. Both procedures resulted in a reduction in the number of antiglaucoma medications, with CW-CPC demonstrating more stable outcomes throughout the follow-up period. In addition, there was a decrease in the number of patients requiring oral acetazolamide at the final follow-up in both groups. Complications were higher in the CW-CPC group compared to MP-CPC, which can be attributed to thermal damage to surrounding tissue caused by the laser. The low number of subjects and retrospective nature of this study need to be taken into consideration when interpreting and generalizing the findings (12).

Limitations

The small sample sizes in most studies prevent us from generalizing the results to the broader population. Furthermore, there was a limited number of RCTs, with most studies being prospective or retrospective cohorts. This could introduce bias in patient selection and affect the results. While complication rates consistently favored MP-CPC in all studies, the outcomes related to success rates and IOP reduction were not consistently uniform as some studies reported comparable or even worse results compared to CW-CPC. The lack of standardization in laser parameters for MP-CPC and different definition of successful cyclophotocoagulation may have contributed to the variability in results.

Conclusion

MP-CPC, as an alternative to CW-CPC, has shown promising results in the treatment of both refractory and non-refractory glaucoma in the adult population. With comparable results in IOP reduction and fewer instances of serious ocular complications, MP-CPC may open new possibilities for cyclophotocoagulation procedures to be used in the earlier stages of glaucoma, rather than exclusively in advanced, end-stage conditions. However, its efficacy in the pediatric population and for NVG remains less defined, as some studies have reported lower success rates in the MP-CPC group compared to the more conventional CW-CPC procedure. This warrants further well-designed RCTs to confirm these findings and establish optimal laser parameters for different types of glaucoma and specific populations of glaucoma patients.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – C.A.P.J.; Design – C.A.P.J.; Supervision – C.A.P.J.; Resource – L.B.; Materials – L.B.; Data Collection and/or Processing – C.A.P.J., L.B.; Analysis and/or Interpretation – C.A.P.J.; Literature Search – C.A.P.J.; Writing – C.A.P.J.; Critical Reviews – C.A.P.J., L.B.

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