Micropulse Versus Continuous Wave Transscleral Cyclophotocoagulation in Refractory Pediatric Glaucoma

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Purpose: The aim of this study was to compare the safety and efficacy of micropulse cyclophotocoagulation (MP-CPC) and transscleral continuous wave cyclophotocoagulation (CW-CPC) for the treatment of refractory glaucoma in the pediatric age group.

Methods: This prospective study included 45 eyes of 36 children requiring transscleral cyclophotocoagulation, in the period spanning from September 2016 to August 2017, using micropulse (MP-CPC) or continuous wave (CW-CPC) modes. The intraocular pressure (IOP) reduction, success rates, and complications were compared for both groups. Success was defined as an IOP of 5 to 21 mm Hg, in the absence of vision-threatening complications at 6 months.

Results: The MP-CPC group included 17 eyes, in patients aged 67.8 ± 48 months, and the CW-CPC group included 28 eyes, in patients aged 61.3 ± 38.3 months. There was a tendency toward lower IOP in the MP-CPC group at all follow-ups, almost reaching statistical significance at 2 weeks and 3 months ($P = 0.05$). IOP reduction was 63% in the MP-CPC group and 67% in the CW-CPC group ($P = 0.6$). The success rate was higher in the MP-CPC group (71% vs. 46% in the CW-CPC group), but the difference was not significant ($P = 0.1$). No significant complications were noted in the MP-CPC group whereas, in the CW-CPC group, 1 eye developed phthisis bulbi, and 2 eyes had severe pain and uveitis ($P = 0.3$).

Conclusions: Both the MP-CPC and CW-CPC are effective in lowering the IOP in children with refractory glaucoma. However, the rate of complications, pain, and inflammation seem to be lower with the micropulse mode, making it a safer alternative for cyclophotocoagulation, especially since retreatments are often needed.

Key Words: micropulse laser, cyclophotocoagulation, pediatric glaucoma

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The management of glaucoma in children is very challenging, with many patients requiring multiple surgeries, often ending in cyclodestructive procedures. Diode laser cyclophotocoagulation is the current standard cyclodestructive treatment used in children in whom incisional surgeries failed, are not applicable, or are expected to fail (eg, in the presence of extensive conjunctival scarring).[1] The 810 nm semiconductor laser (Oculight SLx; Iridex, Mountain View, CA) targets the melanin pigment in the ciliary epithelium, using a continuous wave, resulting in reduction of aqueous secretion. Histologically, the laser energy causes fragmentation and detachment of the epithelium of the ciliary processes and destruction of the ciliary body vasculature.[2] Although the diode laser has good penetration, the continuous wave cyclophotocoagulation (CW-CPC) has been shown to cause significant collateral damage to adjacent structures including the ciliary stroma and ciliary muscle.[3] This can result in postoperative complications such as iridocyclitis, choroidal effusion, loss of vision, chronic hypotony, and phthisis bulbi.[4]

The micropulse mode of laser delivery was initially introduced for retinal laser photocoagulation.[5] In the micropulse mode, the laser is broken into repetitive pulses of laser application, separated by rest periods, allowing gradual build-up of heat energy in the cells treated. This allows protein denaturation to occur faster than the cells' compensatory healing mechanism, which could explain why the micropulse laser can cause biological stress, or even apoptosis in the absence of necrosis. When used transsclerally on the ciliary body, thermal relaxation allowed by micropulse laser prevents extensive tissue disruption in the ciliary processes, epithelium, and adjacent tissues.[6] The Micropulse CPC (IRIDEX, CYCLO G6; Glaucoma Laser System, Mountain View, CA) has recently shown promising results in the management of glaucoma, with possibly fewer complications than those reported with the CW-CPC.[7–12] The purpose of this study was to compare both techniques in the pediatric age group.

PATIENTS AND METHODS

A prospective interventional institutional study was conducted on children below 12 years of age with uncontrolled glaucoma. All eyes requiring cyclophotocoagulation in the period spanning between September 2016 and August 2017 at Abureish Children's Hospital, Cairo University, were included.

The use of the micropulse cyclophotocoagulation (MP-CPC) depended on the availability of the G6 probe in the hospital; when not available, the CW-CPC was used.

The following data were recorded for each patient: age, sex, laterality, type of glaucoma, previous surgeries/lasers, preoperative and postoperative intraocular pressure (IOP) measured by Perkins tonometer, number of glaucoma medications, uncorrected and best-corrected visual acuity when possible, as well as slit lamp and fundus examination. Corneal diameter and axial length were measured preoperatively, then every 3 months postoperatively, using a caliper and A-scan ultrasonography, respectively. Visual field testing was not performed, as most patients had very poor vision. Ocular ultrasonography was performed when needed. In younger children who could not be examined while awake, examination was carried out under chloral hydrate sedation.

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Postoperative complications were documented. Hypotony was defined as IOP < 5 mm Hg.

The study was approved by Cairo University research ethics committee and followed the tenets of the Declaration of Helsinki. A written informed consent was obtained from the patients' parents. All laser procedures were performed under general anesthesia, using sevoflurane.

MP-CPC Group

The IRIDEX Cyclo G6 laser was used with a setting of 2000 mW of 810 nm infrared diode laser with a duty cycle of 31.3%, which translated to 0.5 ms of "on time" and 1.1 ms of "off time." The probe was applied with a firm pressure, perpendicular to the sclera, with the edge of the probe directly on the limbus at all times. The probe was moved in a continuous sliding motion in the superior and inferior quadrants, avoiding the 3 and 9 o'clock meridians. The treatment time ranged from 100 to 120 seconds.

CW-CPC Group

The IRIDEX G-probe was used starting with a power of 1500 mW and duration of 1500 ms. Transillumination with a light source in a darkened theater was used to accurately locate the position of the ciliary body, and the concave side of the footplate was then aligned with the anterior edge of the ciliary body. The power and duration of the laser application was increased until a popping sound was heard. The number of popping shots was left at the discretion of the treating physician. Approximately 15 shots were delivered in the superior quadrants and 15 in the inferior quadrants, avoiding 3 and 9 o'clock positions.

Postoperatively, eyes from both groups received topical prednisolone 1% hourly on the day of the procedure, then qds for 1 week, and bd for 1 week. Cycloplegic eye drops were given tds for 1 week, and systemic NSAIDs for 3 to 5 days. Patients were kept on their antiglaucoma treatment, which was tapered according to the reduction in IOP. Patients were seen 1 week, 2 weeks, 1 month, 3 months, and 6 months after the laser treatment, with more frequent follow-ups when needed.

Complete success was defined as an IOP of 5 to 21 mm Hg at the last follow-up visit, with no other signs of glaucoma progression (increasing corneal diameter, axial length, or cup to disc ratio). Qualified success was defined as an IOP < 21 mm Hg on medications in addition to at least 20% reduction in IOP and/or a reduction in the number of medications used. Failure was considered if these criteria were not achieved, or if a subsequent glaucoma procedure or cyclophotocoagulation was needed to control the IOP, or if a devastating complication occurred (eg, chronic hypotony, loss of > 2 lines of vision, phthsis bulbi). Patients received a single treatment session; in patients requiring another intervention, the final follow-up visit was considered to be the one just before the subsequent intervention.

The primary outcome measure was the rate of complications. Secondary outcome measures were the IOP, number of glaucoma medications, and the rates of success.

Statistical Analysis

Statistical analysis was performed with SPSS for Windows version 15.0.1 (SPSS Inc., Chicago III, IL). Demographic data and preoperative data for both groups were analyzed with the independent *t* test or the Fischer exact test. IOP comparisons between the 2 groups were analyzed with the independent *t* test. Rates of surgical success were analyzed by the Fischer exact test. A *P*-value of <0.05 was considered significant. For survival analysis of surgical success, we used the Kaplan-Meier survival plots, to show the difference of survival probability between the 2 procedures, with the Mantel-Cox logrank test.

RESULTS

A total of 45 eyes of 36 patients, comprised of 17 eyes of 13 patients in the MP-CPC group and 28 eyes of 23 patients in the CW-CPC group, were included in the study. Table 1 shows the demographic and ocular data in the 2 groups. In the MP-CPC group, 15 eyes (88%) had previously undergone continuous wave transscleral diode cyclophotocoagulation, compared with 14 eyes (50%) in the CW-CPC group ($P = 0.01$). The number of previous laser sessions ranged from 1 to 4 times (average 1.6 ± 0.9 and 1.9 ± 1, respectively).

All eyes were seen over a follow-up period of 6 months or until the failure criteria were reached. There was a significant reduction in IOP and glaucoma medications in both groups at all postoperative follow-ups. IOP and glaucoma medications were compared for both groups at 2 weeks, 1 month, 3 months, and 6 months (Table 2). There was a tendency toward lower IOP in the MP-CPC group at all follow-ups, almost reaching statistical significance at 2

TABLE 1. Demographic and Ocular Data

Parameters [N (%)]	MP-CPC Group	CW-CPC Group	*P*
Eyes	17	28	
Right	9 (53)	9 (32)	0.1
Bilateral	15 (88)	22 (78)	0.4
Positive consanguinity	6 (35)	20 (71)	0.02
Positive family history	1 (6)	5 (18)	0.2
Sex			
Male	11 (65)	14 (50)	0.9
Diagnosis			
PCG	11 (64)	15 (53)	0.5
Aphakia/pseudophakia	3 (18)	9 (32)	0.5
Aniridia	2 (12)	1 (4)	0.5
Peter's anomaly	1 (6)	0	0.4
Microspherophakia	0	2 (7)	0.5
Sturge Weber		1 (4)	1.0
Previous surgeries			
Goniotomy	3 (18)	0 (0)	0.05
Trabeculotomy	7 (41)	7 (25)	0.3
Trabeculectomy	7 (41)	17 (61)	0.2
Combined trabeculotomy	2 (12)	2 (7)	0.6
GDD	4 (24)	5 (18)	0.6
CW-CPC	15 (88)	14 (50)	0.01
None	0	4 (14)	0.3
Age at presentation (mo)			
Range	0-120	0-75	0.3
Mean ± SD	7.6 ± 29	16.4 ± 25.4	
Age at surgery (mo)			
Range	8.9-147	2.3-126.8	0.6
Mean ± SD	67.8 ± 48	61.3 ± 38.3	
Cup to disc ratio			
Range	0.9-1	0.3-1	0.02
Mean ± SD	0.9 ± 0.03	0.7 ± 0.2	

CW-CPC indicates continuous wave cyclophotocoagulation; GDD, glaucoma drainage device; MP-CPC, micropulse cyclophotocoagulation; PCG, primary congenital glaucoma.

TABLE 2. Intraocular Pressure and Glaucoma Medications

	MP-CPC Group	CW-CPC Group	*P*
Intraocular pressure (mm Hg)			
Preoperative			
No. eyes	17	28	0.7
Range	13-44	17-45	
Mean ± SD	28.3 ± 8.2	27.5 ± 6.1	
2 wk			
No. eyes	17	28	0.05
Range	3-20	2-26	
Mean ± SD	12.1 ± 4.7	15.9 ± 6.8	
1 mo			
No. eyes	17	28	0.7
Range	2-34	5-38	
Mean ± SD	16.8 ± 7.3	17.7 ± 8	
3 mo			
No. eyes	16	27	0.05
Range	10-22	2-38	
Mean ± SD	15.5 ± 3.7	19.4 ± 8.4	
6 mo			
No. eyes	15	19	0.3
Range	10-25	10-30	
Mean ± SD	16.4 ± 4.6	17.9 ± 5.6	
No. medications			
Preoperative			
Range	2-4	0-4	0.5
Mean ± SD	2.5 ± 0.6	2.3 ± 0.9	
2 wk			
Range	0-4	0-4	0.02
Mean ± SD	2.2 ± 0.9	1.3 ± 1.4	
1 mo			
Range	0-3	0-4	0.2
Mean ± SD	1.7 ± 0.8	1.25 ± 1.2	
3 mo			
Range	0-4	0-3	0.3
Mean ± SD	2 ± 1	1.4 ± 1.1	
6 mo			
Range	0-4	0-4	0.3
Mean ± SD	2.3 ± 0.9	1.7 ± 1.3	

CW-CPC indicates continuous wave cyclophotocoagulation; MP-CPC, micropulse cyclophotocoagulation.

weeks and 3 months ($P = 0.05$). The number of medications were, however, lower in the CW-CPC group, reaching statistical significance at 2 weeks ($P = 0.02$).

The IOP reduction in the MP-CPC group was 63% ± 28%, and, in the CW-CPC group, it was 67% ± 25%, at 6 months ($P = 0.6$).

Success Rates

At the final follow-up, 1 eye (6%) was classified as complete success in the MP-CPC group, and 5 eyes (29%) failed, 2 because of uncontrolled IOP on medications, 2 because of the need for repetition of the laser treatment, and 1 eye because the IOP reduction was <20%, with no reduction in medications. In the CW-CPC group, 5 eyes (18%) were classified as complete success and 15 eyes (54%) as failures. Six failures were due to the need for more laser procedures, 5 went on to have a glaucoma implant, 1 eye had <20% IOP reduction with no reduction in medications, one eye had severe hypotony ending in phthisis bulbi, and 2 failed because of uncontrolled IOP on full medications (Fig. 1). The difference in failure rates between both groups was not significant ($P = 0.1$).

Kaplan-Meier survival analysis was carried out to compare the survival rates between the 2 treatment groups

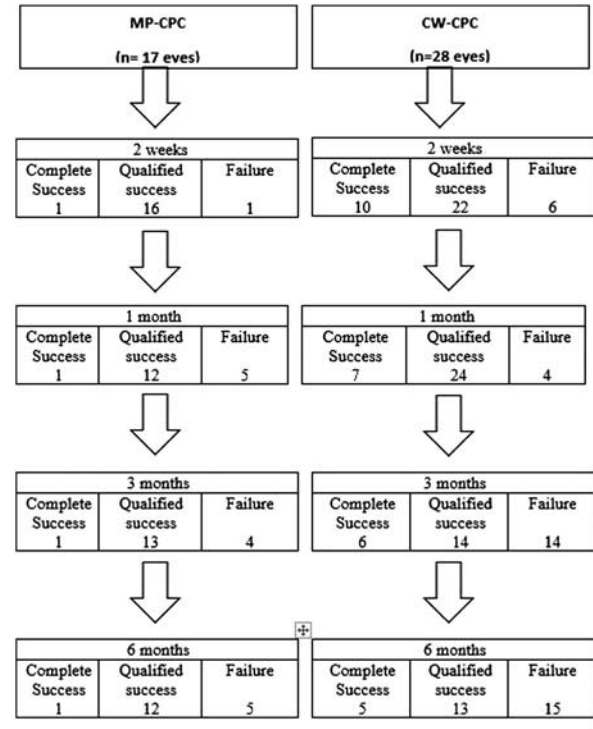

FIGURE 1. Success rates at different follow-ups. CW-CPC indicates continuous wave cyclophotocoagulation; MP-CPC, micropulse cyclophotocoagulation.

(Fig. 2). The mean survival time for the MP-CPC group was 4.7 months (SE, 0.51, 95% confidence interval, 3.7-5.7 mo), while for the CW-CPC group it was 3.4 months (SE, 0.48, 95% confidence interval, 2.5-4.39 mo) ($P = 0.09$).

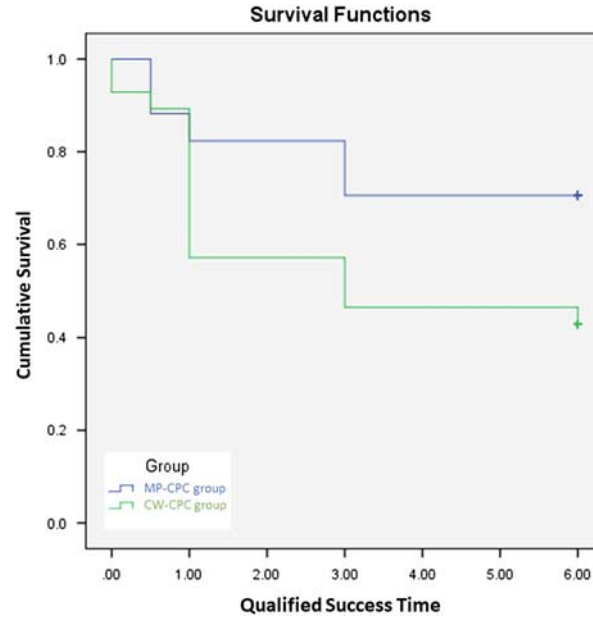

FIGURE 2. Kaplan-Meier survival analysis for qualified success in both groups. CW-CPC indicates continuous wave cyclophotocoagulation; MP-CPC, micropulse cyclophotocoagulation. Figure 2 can be viewed in color online at www.glaucomajournal.com.

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TABLE 3. Results of Studies on Transscleral Cyclophotocoagulation in the Pediatric Age Group Compared With the Current Study

	Design	No. Eyes	Minimum Follow-Up (mo)	No. Treatments (Mean ± SD)	Inclusion	Age (y) (Mean ± SD)	Success Criteria	Success Rates: One Session (%)	Success Rates: Multiple Sessions (%)	Complications	Comments
CW-CPC											
Bock et al[19]	Retrospective	26	6	Single	≤ 10-y old	—	IOP ≤ 21 mm Hg or laser repetition	38	50	RD (1 eye) Loss of vision (4/22 eyes)	70% needed retreatment at least once until final follow-up
Kraus et al[20]	Retrospective	72	—	Multiple (2.29 ± 2.1)	< 18-y old	7.6 ± 5.5	IOP < 21 mm Hg	55	67.6	—	Median time to failure of the initial procedure was 623 ± 620 d
Autrata and Rehurek[21]	Retrospective	69	12	Multiple	< 15-y old	6.1 ± 4.3	IOP ≤ 21 mm Hg	46	79	RD (2 eyes) Choroidal detachment (4 eyes) Uveitis (9 eyes)	Shorter duration of effect in patients <5-y old Aphakic eyes had more sustained IOP control
Kirwan et al[14]	Prospective case series	77	12	Multiple (2.3)	< 18-y old	—	IOP ≤ 21 mm Hg	37	72	RD (3 eyes) Severe inflammation (5.5%)	Aphakic eyes had more sustained IOP control All RD in aphakic eyes
Hamard et al[22]	Retrospective	28	2	Multiple	5-26 y with PCG, anterior segment dysgenesis or secondary aphakic glaucoma	10.7 ± 7.1	IOP from 6-20 mm Hg	—	54.4 at 6 mo 27.7 at 1 y	Decrease in visual acuity (14.3%), inflammation (25.5%), and phthisis (3.5%)	One third of the eyes retreated at least once
Current study (CW-CPC group)	Prospective	28	6	Single	< 12-y old	5.2 ± 3.2	IOP 5-21 mm Hg	46	—	Hypotony (3 eyes) of which one ended in phthisis 2 eyes had severe inflammation	More pain, inflammation, and vision-threatening complications, compared with the MP-CPC group

TABLE 3. (*continued*)

	Design	No. Eyes	Minimum Follow-Up (mo)	No. Treatments (Mean ± SD)	Inclusion	Age (y) (Mean ± SD)	Success Criteria	Success Rates: One Session (%)	Success Rates: Multiple Sessions (%)	Complications	Comments
MP-CPC											
Lee et al[11]	Retrospective	9	12	Single	—	—	IOP 5-21 mm Hg and ≥ 20% IOP reduction	22.2		Mild inflammation in 65%	Success rate significantly lower than in adults
Current study (MP-CPC group)	Prospective	17	6	Single	< 12-y old	5.6 ± 4	IOP 5-21 mm Hg	71		Self-limiting hypotony (1 eye)	Similar IOP reduction and success to CW-CPC but fewer complications

CW-CPC indicates continuous wave cyclophotocoagulation; IOP, intraocular pressure; MP-CPC, micropulse cyclophotocoagulation; PCG, primary congenital glaucoma.

Complications

In the MP-CPC group, one eye developed hypotony for 2 weeks postoperatively. The hypotony resolved with conservative treatment, and the eye was classified as having complete success at 6 months.

In the CW-CPC group, 3 eyes developed hypotony, 2 of which resolved spontaneously, while 1 eye ended in phthsis bulbi. Two eyes developed severe pain and anterior uveitis, which improved after 4 and 6 weeks of medical treatment. Although the CW-CPC group tended to have more serious complications, the difference in the rate of complications between both groups was not significant ($P = 0.3$).

DISCUSSION

Cyclophotocoagulation in the pediatric age group has been reported using cyclocryotherapy,[13] transscleral cyclophotocoagulation,[14] and endoscopic cyclophotocoagulation,[15] and, recently, Lee et al[11] reported the results of micropulse laser cyclophotocoagulation in children. In their study comparing MP-CPC in adults with the pediatric age group, the authors concluded that the results were less promising in children than in adults, with 7 of 9 children who received MP-CPC requiring another IOP-lowering procedure within 1 year. They accounted for the low success rate in the pediatric age group (22%) by the higher regenerative ability of the ciliary body in children,[16–18] and the variability in the position of the ciliary body in buphthalmic eyes, hindering accurate localization of the laser beam. Our study showed a 71% success rate in the MP-CPC group, which could be due to the greater extent of treatment in our study (4 quadrants compared with 2 quadrants in Lee and colleagues study study). Although it is expected that the success rate would decrease over time, our 6-month results still showed higher success rates than those previously reported for CW-CPC in the pediatric age group. The CW-CPC group in our study also showed a lower success rate (46%), but the difference was not significant ($P = 0.1$). Table 3 compares the results of previous studies on transscleral cyclophotocoagulation in the pediatric age group with findings from our study. Unlike results from Autrata and Rehurek as well as Kirwan and colleagues, aphakic eyes in both groups in our study did not fare better than other types of glaucoma.

The main concern with cyclodestructive procedures is the risk of complications, many of which are vision threatening. Inflammation, hypotony, choroidal detachment, macular edema, sympathetic ophthalmia, and phthisis bulbi are among the complications encountered, which may lead to reluctance in resorting to such procedures and tendency to reserve them for eyes with very poor vision. Williams et al[12] reported a relatively high rate of complications in their study on MP-CPC in refractory glaucoma, when they used a "stop-and-go" pattern for laser application, wherein the probe was held in place for 10 seconds, before moving to treat the adjacent section of perilimbal conjunctiva, over a period of 120 to 360 seconds. They reported hypotony in 8.8% of eyes, corneal edema in 2%, prolonged anterior chamber reaction for > 3 months in 26%, and phthisis in 2%. We applied the micropulse laser over a 100 to 120 second period in a continuous sliding motion and did not encounter any serious complications in the MP-CPC group. One of the 17 eyes developed hypotony, which resolved spontaneously and ended up being controlled on no medications. None of the patients treated had pain or photophobia. We did not grade the conjunctival hyperemia postoperatively, but it was felt to be much less in the MP-CPC group, with most eyes looking quiet on

the first day after the procedure. This was not the case in the CW-CPC group, wherein many eyes were photophobic, with moderate to severe hyperemia. Two eyes in the CW-CPC group had severe pain and inflammation that persisted for 4 and 6 weeks, 3 eyes developed hypotony with 1 eye ending in phthisis bulbi. The lower risk of complications with MP-CPC corresponds well to that reported in previous studies. Lee et al[11] did not encounter any complications in pediatric eyes treated with MP-CPC, apart from some mild early inflammation. Aquino et al[8] compared MP-CPC with CW-CPC in adults with refractory glaucoma and reported a lower rate of complications with the micropulse group. Prolonged inflammation was more frequent in their CW-CPC group (30%) compared with 4% in the MP-CPC group, with 1 eye in the CW-CPC group going into phthisis bulbi. No pain was reported postoperatively, in 100% of their patients in the MP-CPC group, compared with 86% in the continuous wave group.

We used the same intensive postoperative steroid regimen in both groups to standardize the effect of possible steroid response; however, in light of findings concerning the lower rate of postoperative inflammation in the MP-CPC group, we would consider a less intensive postoperative treatment for micropulse cases in the future.

Our study has some limitations. A significantly higher number of eyes had previously undergone CW-CPC in the MP-CPC group compared with the CW-CPC group (88% and 50%, respectively). This could have influenced the results in the MP-CPC group adversely, as these eyes may be more resistant to cyclophotocoagulation, or may have higher regenerative ability of the ciliary processes. We only looked at the results of a single treatment with both the micropulse and continuous wave modes. It would be useful to study the results of multiple treatments with the micropulse mode in children, as well as the effect of alternating treatments between MP-CPC and CW-CPC, to determine whether the repetition of laser sessions would achieve higher success rates, with a lower risk of complications than those reported with CW-CPC.

It would have been useful to grade the anterior uveitis postoperatively and compare it in both groups; however, because most children were only examinable with a portable slit lamp, this was not possible. The short follow-up period, the relatively small sample size, and the use of Perkins tonometer to assess the IOP were also limitations to the study.

In conclusions, our results showed that both the MP-CPC and CW-CPC have similar efficacy in the pediatric age group, yet the micropulse mode resulted in a lower rate of complications, and less postoperative inflammation and pain, which can make it a safer option for retreatments.

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