



TECHNICAL TALK

MICROPULSE TRANSSCLERAL CPC: AN EVIDENCE REVIEW



Exploring the ideal laser energy parameters and potential dose-dependent effect.

BY FACUNDO G. SANCHEZ, MD; AND TOMÁS M. GRIPPO, MD

Micropulse transscleral cyclophotocoagulation (TSCPC) is a novel technique that uses repetitive micropulses of diode laser energy, delivered with the Cyclo G6 Glaucoma Laser System (Iridex), in an off-and-on cyclical fashion. It has been proposed that the *off* periods allow thermal dissipation, causing less collateral damage than traditional continuous-wave TSCPC.^{1,2} However, neither the exact mechanism of action (MOA) of micropulse TSCPC nor the ideal parameters for an optimal balance between efficacy and safety have been fully elucidated.

It is possible that the micropulse technology exerts its IOP-lowering effect through a combination of more than one MOA, including (1) sub-threshold cell damage, mainly at the level of the pigmented epithelium and indirectly to the nonpigmentary epithelium of the ciliary body, with no visible scarring²; (2) uveoscleral outflow increase through extracellular matrix remodeling³; and (3) a pilocarpine-like effect recently proposed by Murray Johnstone, MD, based on an experimental study on enucleated monkey eyes.⁴ This study in particular may have untapped potential to help explain, at least to some extent, the possible

dose-dependent effect of micropulse TSCPC, which becomes more visible after comparing clinical studies that used different amounts of energy.⁵

This article reviews the available evidence to help approximate the ideal laser energy parameters to achieve the best balance of efficacy and safety and to further explore the evidence of a dose-dependent effect.

MOA AND CLINICAL IMPLICATIONS

Subthreshold cell damage, reduced collateral damage, and clinical impact. As previously stated, results of clinical and experimental studies suggest that the *off* periods in micropulse TSCPC restrict the accumulation of caloric energy in the tissues adjacent to the pigmented epithelium. This allows thermal dissipation, preventing the surrounding tissues from reaching coagulation temperatures and therefore reducing collateral damage.^{1,2,6,7}

The clinical impact of this modified surgical technique was shown in a study by Aquino et al⁶ that compared the efficacy and safety of micropulse TSCPC and continuous-beam TSCPC in a prospective cohort of 48 patients. In this study, 24 patients were treated with micropulse TSCPC and 24 with continuous-wave TSCPC. Success was defined as an IOP between 6 mm Hg

and 21 mm Hg and at least a 30% decrease in IOP from baseline.

At 18 months, the investigators found no statistically significant difference in efficacy between the groups (52% for micropulse TSCPC vs 30% for continuous-wave TSCPC; $P = .13$). They did, however, find a statistically significant difference in safety in favor of micropulse TSCPC ($P = .01$). Prolonged hypotony (IOP ≤ 5 mm Hg for more than 6 months) was observed in five eyes treated with continuous-wave TSCPC and no eyes treated with micropulse TSCPC. Visual acuity decreased by 9% (2/23) in the continuous-wave group and 4% (1/23) in the micropulse group.

Prolonged inflammation of the anterior chamber was observed in 30% (7/23) of the continuous-wave patients and 4% (1/23) of the micropulse patients. The investigators observed phthisis bulbi in 4% (1/23) of the continuous-wave patients and 0% in the micropulse patients and scleral thinning in 17% (4/23) of the continuous-wave patients and 4% (1/23) of the micropulse patients.⁶

Uveoscleral outflow increase. In 1994, Liu et al⁸ observed an increase in uveoscleral outflow after continuous-wave Nd:YAG laser TSCPC. Recently, Barac et al³ published a study of

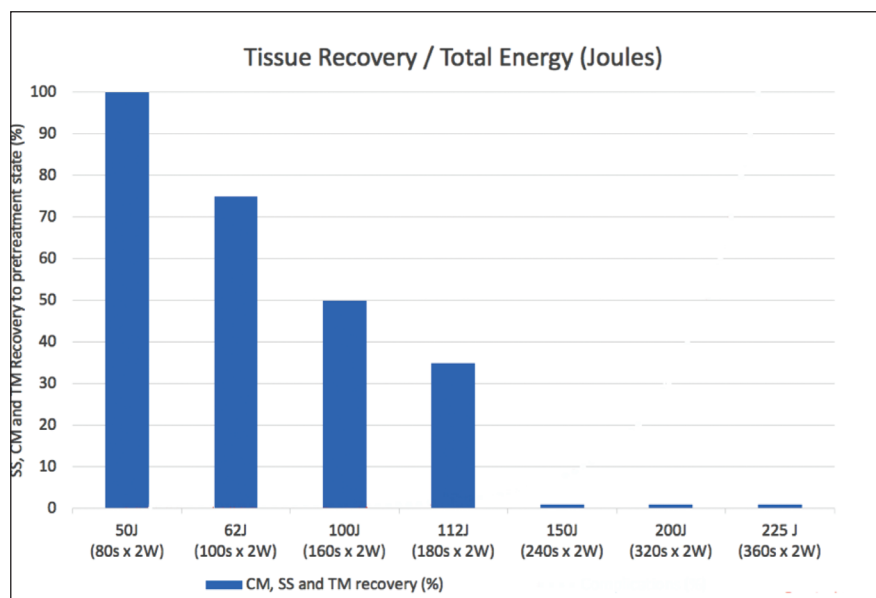


Figure 1. Blue bars represent an approximation of the progressively decreasing recoil/relaxation of the scleral spur, ciliary muscle, and trabecular meshwork with increasing energy levels observed in the experimental study by Johnstone et al.⁴ (Courtesy of Sanchez et al⁵).

22 glaucomatous eyes treated with micropulse TSCPC in which choroidal thickness was measured using OCT. They found that patients who were successfully treated with micropulse TSCPC had an average increase in choroidal thickness of 16 mm at 6 months—from 369 mm at baseline to 385 mm after treatment. In contrast, patients who did not respond had no choroidal thickening after the intervention. Although this was an interesting finding, the series of cases was too small to show statistical significance. After these observations, the authors theorized that choroidal thickness variation may be the result of a rise in uveoscleral outflow after micropulse TSCPC.

Pilocarpine-like effect. This MOA for micropulse has recently been proposed by Johnstone et al after an experimental study on monkeys.⁴ According to the authors, micropulse acts on the longitudinal fibers of the ciliary muscle, causing contraction of the fibers and therefore displacement of the scleral spur in a posterior and inward direction. This, in turn, modi-

fies the configuration of the trabecular meshwork and the conventional outflow track of the aqueous humor. The effect is similar to that of pilocarpine, which causes enlargement of the trabecular spaces and expansion of the Schlemm canal area, reducing the tendency toward collapse or narrowing of the canal lumen and thus facilitating the drainage of aqueous humor.⁴

Johnstone et al's technique involved the application of micropulse TSCPC laser treatments by placing the probe in 63 treatment spots in a circumferential distribution throughout the eye, instead of the sweeping motion widely used in published micropulse TSCPC clinical studies. The authors stated that a typical clinical equivalent was ~1.59 J per probe location and a total of ~100 J per eye. The joule (J) is a unit of energy measurement that is equal to the total treatment time in seconds (s), times the power in watts (W), times the duty cycle, which, in turn, can be divided by the number of probe locations (in this case, 160 seconds of treatment duration, 2 watts of power, 31.3% duty cycle,

and 63 probe locations, resulting in ~1.59 J). They tested an energy range of 0.75 J to 2.35 J per probe location (a total of approximately 47–150 J per eye), which is 50% lower and 50% higher than the aforementioned clinical equivalent. The authors reported progressively less recovery of the contraction of the longitudinal fibers of the ciliary muscle to the pretreatment state (ie, a greater permanence of the pilocarpine-like effect) with increasing energy levels (Figure 1).⁴

Sanchez et al⁵ searched the literature for all published clinical studies with micropulse laser and compared the energy settings used and outcomes with the experimental data of Johnstone et al. They found interesting coincidences, as described below.

IDEAL PARAMETERS AND DOSE-DEPENDENT EFFECT

The findings of Johnstone et al⁴ may explain, to some extent, why the IOP-lowering effect of TSCPC seems to positively correlate with the amount of total energy applied.

Sanchez et al⁵ published a literature review describing the outcomes of all published clinical studies and experimental data using micropulse TSCPC that employed different energy levels, ranging from 62 J to 225 J. This review was undertaken after the authors published their initial experience with micropulse TSCPC in 22 eyes (mostly congenital and pseudoexfoliation), in which they observed a trend toward higher success rates in eyes that had been treated with more energy (112 J) compared with those treated with 100 J or 62 J, at 7.9 months of follow-up. They also noted that, with lower energy settings, the initial IOP-lowering effect dissipated over time.⁹

In the literature review, Sanchez and coworkers transformed the laser parameters employed in each clinical study to joules to facilitate interpretation. They noted that the studies in which energy levels between 112 J and

150 J were applied obtained a good balance between efficacy and safety, defined as a moderate IOP decrease of around 35% with few or no complications.⁵ Energy levels lower than 100 J caused no side effects but yielded lower IOP reductions and shorter survival of effect. In contrast, with energy levels higher than 200 J (320 s x 2 W x 0.313 duty cycle), greater IOP reduction was reported, but complications were much more frequent.^{10,11}

Based on these findings, Sanchez et al⁵ suggested that the experimental results published by Johnstone et al⁴ may allow further narrowing of the optimal laser energy levels. In that experimental study, the pilocarpine-like effect was maximum and permanent at around 150 J (2.35 J per probe location), roughly equivalent to a clinical setting of 240 s x 2 W x 0.313 duty cycle. Coincidentally, the clinical studies that used similar energy levels—close to 150 J—obtained moderate IOP decreases of around 30% with few or no complications.⁹ Based on these data, Sanchez et al hypothesized that, with current surgical technique and commercially available probes, the ideal laser parameters for micropulse TSCPC might converge in a mid-range level, between 112 J and 150 J, with experimental data orienting to a point closer to 150 J (Figure 2). This is only an initial hypothesis based on the limited published literature so far, in which the authors found gross coincidences in the observed data.

Recently, Quigley et al¹² published retrospective results with different energy levels using continuous-wave diode laser TSCPC. They obtained significantly better results with 135 J per treatment than with 98 J ($P = .0009$). In addition, those authors observed a dose-response relationship with this technique. Given the technique's similarity with micropulse TSCPC, it is reasonable to expect these coincidences. This evidence is in accordance with the hypothesis of Sanchez et al.⁵

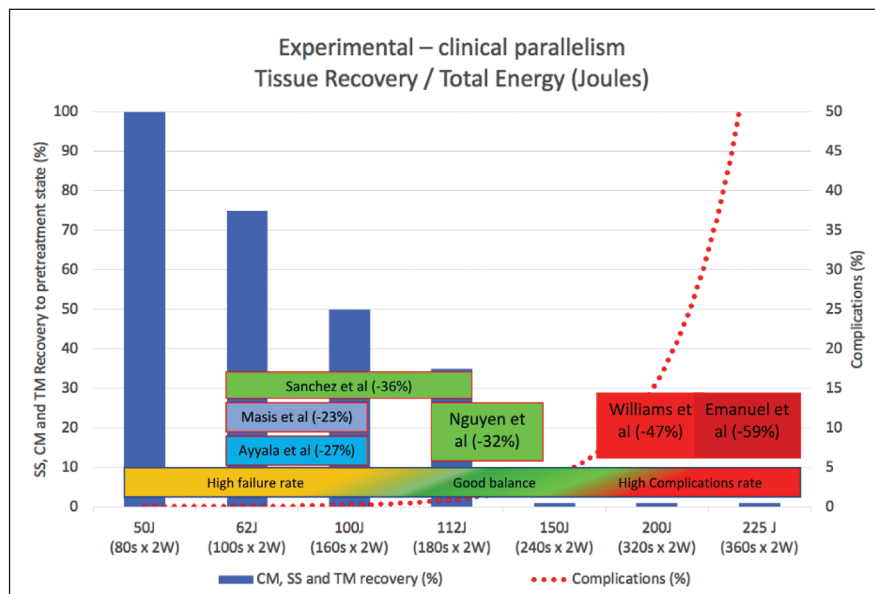


Figure 2. Experimental and clinical data overlap. The x-axis shows increasing energy levels in joules. The blue bars on the y-axis summarize the progressively lower recoil or relaxation of the scleral spur (SS), ciliary muscle (CM), and trabecular meshwork (TM) observed in the experimental study by Johnstone et al.⁴ Color boxes represent the studies that applied the corresponding treatment durations and the mean IOP lowering effect (%) obtained, respectively. The secondary axis represents clinical complications with increasing energy levels reported in the literature. The colored bar illustrates an evidence-based hypothesis of the best balance between efficacy and safety. (Courtesy of Sanchez et al⁵).

The micropulse exerts its effect through a combination of the aforementioned MOAs. It is not unreasonable to hypothesize that maybe one mechanism prevails over another depending on the level of energy used. Perhaps it is in the midrange energy level (112–150 J) that the pilocarpine-like effect is most prominent. At higher energy levels, the cyclodestructive effect of the laser might become the main mechanism, explaining the higher complication rates reported.^{10,11}

It would be helpful to have a guideline, based on the potential dose-response effect, that proposes defined energy parameters while taking into account the individual characteristics of each patient. This could provide surgeons with greater certainty regarding the balance between efficacy and safety that might be expected, as well as the survival of the treatment's effect. Depending on the scenario and available options, surgeons could opt for more or less aggressive treatments,

commit to the possibility of having more or fewer side effects, and even choose a temporary duration of the IOP-lowering effect when necessary.

Limitations. It should be noted that the observations regarding dose-response relationship for micropulse TSCPC are a gross estimate. Limitations are numerous, including difficulty interpreting the studies due to the different parameters used, possible variability in surgical technique used, and heterogeneity of the cohorts. Individual characteristics such as pigmentation and type of glaucoma could have an impact on final outcomes. For example, some authors reported higher odds of prolonged inflammation in heavily pigmented eyes (OR, 3.61; 95% CI, 1.27–10.23; $P = .02$), which led them to suggest that it is reasonable to use shorter treatment durations in this population.¹⁰ In patients with congenital glaucoma or highly myopic eyes, anatomic variation may require further exploration (via ultrasound

biomicroscopy analysis) to correctly place the probe over the target tissue. The presence of pseudoexfoliation may also hinder the treatment's success.

CONCLUSION

The literature yields the hypothesis that a dose-response effect for micropulse TSCPC might exist. According to Sanchez et al,⁵ with current technique and commercially available probes, the procedure appears to have a safe zone with a good balance between efficacy and safety in the 112–150 J range, and experimental data suggest a point close to 150 J. When this zone is exceeded, the ophthalmologist may obtain a greater reduction in IOP, but at the cost of more significant side effects. This hypothesis does not consider the individual characteristics of the patient, but it establishes a frame-

work and a starting point to further refine the technique and individualize its application.

Prospective studies are needed to corroborate this hypothesis, evaluate the MOA that prevails at different energy levels, and help create guidelines to determine ideal laser parameters on an individual basis. ■

TOMÁS M. GRIPPO, MD

- Founder, Grippo Glaucoma Center, Buenos Aires, Argentina
- Assistant Professor (Adjunct) of Ophthalmology and Visual Science, Yale University, New Haven, Connecticut
- Financial disclosure: None

FACUNDO G. SANCHEZ, MD

- Research Fellow, Grippo Glaucoma Center, Buenos Aires, Argentina
- facufgs@gmail.com
- Financial disclosure: None

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