Polskie Towarzystwo Okulistyczne
www.pto.com.pl

KLINIKA OCZNA 2021, 123, 4: 203–209
Received: 26.02.2021 Accepted: 4.03.2021

ORIGINAL PAPER

Access this article online

Website:
www.klinikaoczna.pl

DOI:
https://doi.org/10.5114/ko.2021.111821

Anatomical and functional outcomes of treatment for retinopathy of prematurity (ROP) in zone I

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ABSTRACT

Aim: To assess treatment methods of zone I retinopathy of prematurity (ROP) and evaluate anatomical, functional and refractive outcomes of patients after the treatment.

Material and methods: The anatomical outcomes were evaluated retrospectively for all patients born and treated for zone I ROP in the Gynecology and Obstetrics Hospital of Poznan University of Medical Sciences in 2016-2019. Functional and refractive outcomes were assessed for the patients who remained in follow-up after 12 months of corrected age.

Results: Forty-five eyes of 25 patients were included in the study. Two infants (3 eyes, 6.7%) were treated with laser photocoagulation (LP), 8 infants (15 eyes, 33.3%) had ranibizumab injections (IVR), 15 infants (27 eyes, 60.0%) had IVR followed by LP. Forty-one eyes (91.1%) of 23 patients had favorable anatomical outcomes characterized by an attached retina and plus disease regression. In 34 eyes of 19 patients, visual reactions, visual acuity (VA), and refractive error were assessed. The mean follow-up time was 36 ±17.4 months (16-64 months). In 17 patients (89.5%), visual responses were present. The mean VA for the 9 eyes tested with Lea optotypes was logMAR 0.5±2.4 (0.5-0.1). The cycloplegic autorefractor measurements revealed: hyperopia in 2 eyes, physiological hyperopia/emmetropia in 8 eyes, myopia in 24 eyes.

Conclusions: Both anatomical and functional results of zone I ROP treatment in our medical center seem satisfactory. This validates the careful use of IVR as a first-line treatment in zone I ROP. Refractive measurements revealed a high number of myopic eyes both in children treated with IVR alone and in those treated with IVR with deferred LP.

KEY WORDS: zone I retinopathy of prematurity, ROP, anti-VEGF injections, laser photocoagulation, anatomical functional and refractive outcomes.

INTRODUCTION

Treatment of retinopathy of prematurity (ROP), especially in zone I, is still a challenge. As intensive neonatal care is developing, a growing number of infants, including those born as early as 23 weeks of gestational age (GA), survive. In Poland, approximately 28,000 infants are born preterm every year (7% of all infants born), about 1200 with extremely low birth weight (BW) below 1,000 g, and GA below 28 weeks[1]. The number of premature children in Poland is high compared to western Europe due to cultural and legal conditions – all infants born ≥ 23 + 0 weeks GA are reanimated and hospitalized. The real success is to plan and conduct such treatment to give them a chance for a full life. In ophthalmology, it means not only to preserve the normal anatomical structure of the eye but to provide a treatment that grants satisfactory functional outcomes.

Extremely preterm infants with low birth weight may develop zone I ROP – a severe form of the disease localized most centrally in the retina. Despite proper screening and timely treatment, the outcomes for ROP zone I are still unsatisfactory worldwide.

International guidelines state which patients should be treated, but the decision on a particular treatment scheme depends on local experience. Current treatment modalities include laser photocoagulation (LP) of the avascular retina and intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents, rarely used cryotherapy, and vitrectomies or scleral buckling for retinal detachment.

The preferences of treatment methods change over time, and to assess them, the evaluation of functional outcomes – visual reactions and visual acuity (VA) – is necessary. It is

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also essential to predict how a particular treatment influences a patient's refraction.

VA testing varies for different age groups. Not many devices are available for quantitative measurements in the group of children below 2.5 years. Therefore, the reports with the most current data that assess both anatomical and functional outcomes in children after zone I ROP treatment are still limited. Few studies from Poland have been published so far. This study analyzes zone I ROP's treatment methods and assesses structural findings, functional outcomes (visual reactions and visual acuity), and refractive errors.

MATERIAL AND METHODS

The study followed the tenets of the Declaration of Helsinki and was approved by the Bioethics Committee of Poznan University of Medical Scienceś (Resolution No. 132/18).

It analyses the results of ROP zone I treatment of the infants born in the Gynecology and Obstetrics Hospital of Poznan University of Medical Sciences between 1 January 2016 and 31 December 2019. The infants were identified through a retrospective review of patients' medical records. The anatomical outcomes were evaluated. Subsequently, the data on functional outcomes and refractive errors were assessed for the patients who had follow-up examinations in the Outpatient Clinic for Preterm Infants of University Clinical Hospital no. 1 in Poznan after 12 months of corrected age. The included patients had regular follow-up visits, at least once a year, the last one less than a year before the analysis.

Screening and treatment

The screening examination for ROP followed the guidelines proposed by the Polish Society of Ophthalmology (≤ 33 weeks of GA, ≤ 1,800 g of BW, or on a decision of a neonatologist) [2]. Findings were classified according to the Revised International Classification of Retinopathy of Prematurity (ICROP) [3]. Treatment criteria were based on Early Treatment for Retinopathy of Prematurity (ETROP) guidelines [4].

The initial treatment was either LP of the avascular retina or intravitreal anti-VEGF injection of ranibizumab (IVR), depending on the stage and localization of the changes and the decision of the treating team. Peripheral retinal ablations were carried out with a diode laser of 810 nm wavelength with confluent burns (Iris Medical OcuLight SL). Anti-VEGF injections were performed with 0.25 mg/0.025 ml ranibizumab (half the adult dose).

Both procedures were performed under general anesthesia. The treatment methods were discussed with the guardians of the patients, and their written informed consent was obtained. After treatment, the patients were examined until the total regression of ROP, stabilization of the changes, or the necessity for retreatment.

Anatomical outcomes

The fundus was evaluated at each examination after treatment. A favorable anatomical outcome was defined as the attached retina at the posterior pole with plus disease regression. An unfavorable anatomical outcome was defined as a retinal detachment involving zone I.

Visual reactions and visual acuity

Positive visual reactions were ascertained if a response to any visual stimuli was present (such as fixing and following the object, making eye contact).

In the group of patients at the age between 12 months and 2.5 years, the Teller Acuity Card assessing grating acuity was used as a gold standard. If a patient could not perform the test (due to lack of interest or irritation) following the moving object – Heidi face – a special paddle with a high-contrast face figure designed by Lea Hyvärinen was tested.

After 2.5 years of age, VA was tested with Lea Hyvärinen optotypes shown on LCD panel from a 5 m distance. Both binocular and monocular VA was tested. If a patient was unable to perform the test, a moving object was shown to assess whether a patient was following it.

Refraction

Cycloplegic refraction (after instillation of 1% cyclopentolate) was performed using a handheld autorefract-keratometer (Retinomax K-plus 3, Righton, Tokyo, Japan). The results were recorded as measurements of the spherical power, cylindrical power and spherical equivalent (SE – spherical plus half of the cylinder power). The refractive errors were divided into categories based on the SE: hyperopia (≥ +3.0 D); physiological hyperopia (+0.5 D to +3.0 D); emmetropia (+0.50 to –0.5 D); myopia (≤ –0.5 D to –5.0 D); high myopia (≤ –5.0 D). The refractive error ≥ +3.0 D was corrected with glasses as recommended by the German Society of Ophthalmology (Deutsche Ophthalmologische Gesellschaft) [5].

Other examinations

After visual function testing, a full eye examination was conducted, including a cover/uncover test, alternate cover test, extraocular movement assessment, and dilated fundal check. The presence of strabismus, nystagmus, and floating eye movements was recorded.

RESULTS

A total of 45 eyes of 25 patients who received treatment due to ROP in zone I were included in the study. In 5 patients ROP in zone II was diagnosed in the fellow eye and treated simultaneously with ROP in zone I, but these eyes were excluded from the analysis. Two infants (3 eyes, 6.7%) were treated with LP, 8 infants (15 eyes, 33.3%) had IVR (in 2 patients – 4 eyes – IVR was given twice), 15 infants (27 eyes, 60.0%) had IVR followed by LP (in 3 patients – 6 eyes – a second injection was administered before the laser treatment).

The mean gestation age (GA) of the patients was 25 ±1 weeks (range: 22-27 weeks) and the mean birth weight (BW) was 775 ±163 g (range: 410-1,080 g). Aggressive posterior ROP (APROP) occurred in 12 patients (22 eyes). The ROP stage at the time of initial treatment is shown in Table I.

Forty-one eyes (91.1%) of 23 patients had favorable anatomical outcomes characterized by an attached retina with regression of plus disease. In 4 eyes (8.9%) of 2 patients an unfavorable anatomical outcome – retinal detachment, despite treatment, was observed. These eyes were not operated on with a vitrectomy due to the advanced stage of ROP.

Nineteen patients remained in continuous follow-up in the Outpatient Clinic for Preterm Infants. Four infants were lost to follow-up (two of them had only one follow-up visit), and 2 patients had bilateral RD. The patient flow diagram is shown in Figure 1.

In 34 eyes of 19 patients who remained in follow-up visual reactions, VA and refractive error were assessed. The mean follow-up time was 36 ±17.4 months (range: 16 months to 5 years and 4 months). The mean corrected age at the last visit was 33 ±17.4 months (range: 13 months to 5 years and 1 month).

In 17 out of 19 patients (89.5%), visual reactions were present. In the group of 10 patients between the age of 12 months and 2.5 years, 2 patients were examined with Teller Acuity Cards. The VA tested was adequate for the age of patients. Seven patients fixed and followed the objects shown. In one patient from this group visual reactions were doubtful (it was a patient with grade IV intraventricular hemorrhage and hemorrhagic hydrocephalus). Five out of 9 patients at the age above 2.5 years had their VA tested with Lea Hyvärinen optotypes shown on the LCD panel. The mean VA for the 9 eyes tested was logMAR 0.5 ±2.4 (range: logMAR 0.5-0.1). Three patients had VA inadequate for their age – they fixed and followed objects from a short distance. As the anatomy of the eyes of these patients was normal, the general state and neurological changes were most likely responsible for the inadequate responses: one of these patients had periventricular leukomalacia and two of them had delayed psycho-motor development. In one patient from this age group, visual reactions were doubtful (it was also a patient with grade IV intraventricular hemorrhage and hemorrhagic hydrocephalus) (Table II).

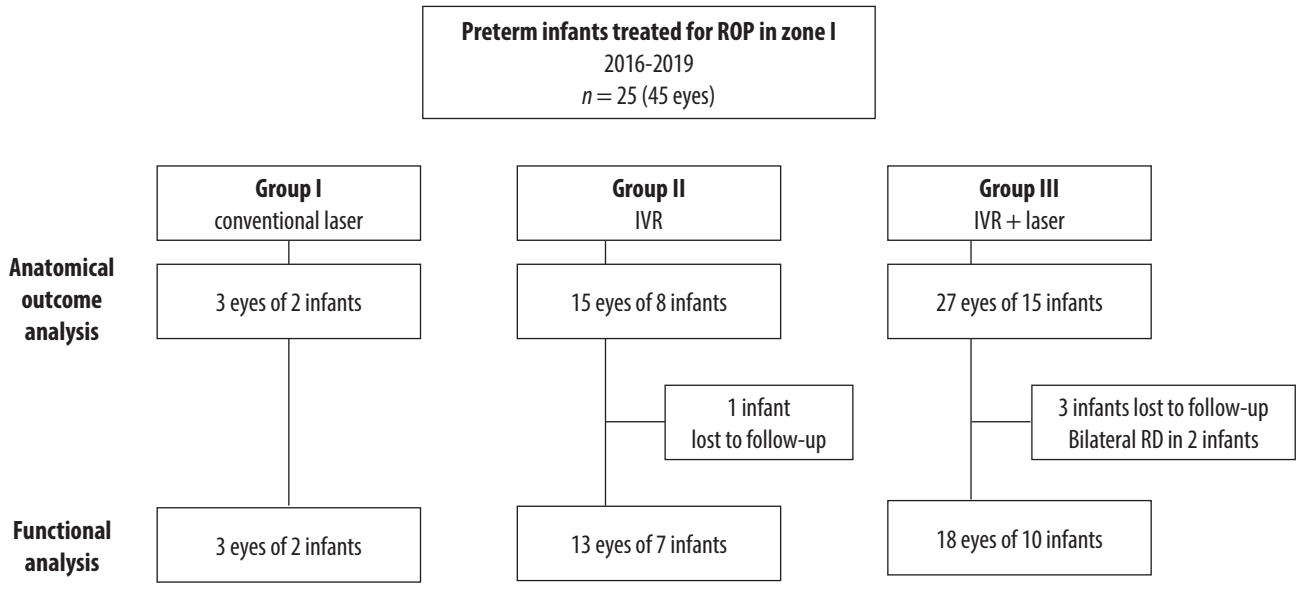
The autorefractor measurements revealed the following refractive outcomes: hyperopia in 2 eyes, physiological hyperopia in 6 eyes, emmetropia in 2 eyes, myopia in 14 eyes, high myopia in 10 eyes. Eight patients had anisometropia (difference in the refractive power > 1.0 D). Mean SE was +2.2 ±1.5 D for hyperopia and −5.0 ±4.7 D for myopia. Thirteen children (68.4%) required refractive error correction: 24 of 34 eyes (70.0%) due to myopia and 2 of 34 eyes (5.9%) due to hyperopia ≥ +3.0 D. Distribution of spherical equivalent refractive error among the 3 groups is shown in Figure 2. One eye from Group I (33.3%), 9 eyes (69.2%) from

Table I. ROP stage at time of initial treatment

Zone, stage, plus disease	Eyes ($n = 45$)	%
APROP	22	48.9
ROP zone I		
stage 1 plus disease	7	15.6
stage 2	2	4.4*
stage 2 plus disease	4	8.9
stage 3	2	4.4
stage 3 plus disease	8	17.8

APROP – aggressive posterior ROP

** treatment applied outside ETROP criteria, on the decision of the treating team*



IVR – intravitreal ranibizumab injection
RD – retinal detachment

Figure 1. Patient flow diagram

Table II. Demographic and clinical characteristics and visual acuity of children who remained in a continuous follow-up

	Corrected age at the last visit (months)	Birth weight (g)	Gestational age (weeks)	ROP treatment	Visual acuity	
					Right eye	Left eye
1	13	1080	27	IVR + laser	Fixes and follows	
2	14	670	24	IVR	Fixes and follows	
3	15	480	23	IVR	–	Fixes and follows
4	16	665	24	IVR + laser	Fixes and follows	
5	17	780	23	IVR + laser	Fixes and follows	
6	17	915	25	IVR	TAC – age appropriate VA	
7	21	705	25	IVR + laser	Fixes and follows	
8	23	775	27	IVR + laser	Fixes and follows	
9	24	410	26	IVR + IVR + laser	Fixes and follows	
10	25	750	23	IVR + laser	TAC – age appropriate VA	-
11	37	805	25	IVR + laser	Doubtful visual reactions	
12	37	785	27	IVR	0.4 logMAR (0.4 decimal)	
13	40	896	26	IVR + laser	Fixes and follows	-
14	51	540	22	IVR	0.5 LogMAR (0.32 decimal)	
15	51	790	25	IVR + IVR + laser	0.1 logMAR (0.8 decimal)	0.5 logMAR (0.32 decimal)
16	55	1040	26	IVR	Doubtful visual reactions	
17	56	860	25	laser	0.5 logMAR (0.32 decimal)	-
18	57	905	25	IVR + IVR	0.4 logMAR (0.4 decimal)	0.3 logMAR (0.5 decimal)
19	61	880	25	laser	Fixes and follows	

"–" eyes excluded from the analysis due to ROP in zone II treatment

TAC – Teller Acuity Cards; IVR – intravitreal ranibizumab injection

Group II, and 14 eyes (77.8%) from Group III were myopic. Mean age at refraction was the same as the mean corrected age at the last visit – 33 months ± 17.4 (range: 13 months – 5 years and 1 month).

The full eye examination revealed strabismus in 6 patients (31.6%), nystagmus in 6 patients (31.6%), and floating eye movements in 2 patients (10.5%).

DISCUSSION

The CRYO-ROP study [6] confirmed in 1988 the effectiveness of ROP treatment. Since then, the treatment methods of ROP have been changing LP becoming a gold stadnard and anti-VEGF intravitreal injections a promising new opition in ROP requiring treatment with no retinal detachment. The treatment methods have been often evaluated, but the analyses have focused mainly on the anatomical outcomes. However, avoiding adverse structural effects is not sufficient to obtain good functional results of ROP treatment. As ROP is a lifelong disease, visual outcomes are crucial for the patients and their families. Therefore, in this study, we assessed both the anatomical and functional results of ROP zone I treatment and refractive error of the patients.

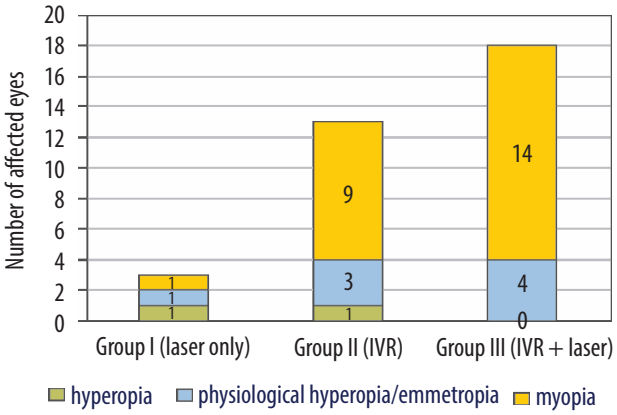
The anatomical outcomes of zone I treatment are generally worse than those of zone II worldwide. Zone I ROP (including APROP) occurs in the ultra-premature infants – in our study all patients with zone I ROP were born ≤ 27 weeks GA with BW ≤ 1,080 g. Zone I ROP is the most dangerous form of the disease – much retina is to be still vascularized, and the risk of retinal detachment extends in time. Effective neonatal care, proper screening, and timely treatment increase the chance of satisfactory treatment results. In our study, good anatomic results were observed in 91.1% of the eyes treated, while retinal detachment occurred in 8.9% of eyes. In our previous study analyzing the treatment by laser photocoagulation and salvage intravitreal ranibizumab injection in the most severe cases of ROP both in zone I and zone II retinal detachment was observed in 22.6% of the eyes [7]. Since that analysis we have changed the treatment protocol and started to use IVR as a first-line treatment. The anatomical results of the present study confirm the validity of this decision.

In the current study only 6.7% of the eyes with zone I ROP were treated with laser as a first-line treatment. This results from the increasing reliance on anti-VEGF injections in zone I ROP. First of all, despite laser photocoagulation

being a gold standard for ROP worldwide [8, 9] especially for zone II ROP, the procedure in zone I consists in difficult photocoagulation close to the macula and usually requires division of the treatment into two stages which involves repeating general anesthesia. Secondly, ROP zone I treatment with laser is often reported as unsatisfactory: the ETROP study reported 27.8% of adverse outcome and BEAT-ROP study documented macular dragging or retinal detachmen in 18 out of 33 eyes (54.5%) after zone I laser treatment.

An increasing trend of anti-VEGF agents use has been observed since the publication of the BEAT-ROP study[10] in 2011. Improved structural outcomes encouraged intravitreal bevacizumab (IVB) and ranibizumab use as first-line therapy. The study by Mintz-Hittner *et al.* [11] showed significantly better structural results of IVB monotherapy in infants with stage 3+ ROP compared with laser ablation for zone I. A conclusion of the recent broad multicenter RAINBOW study was that ranibizumab at 0.2 mg might be superior to laser therapy in ROP treatment [12]. Relatively easy administration, fast regression of neovascularization and plus disease, possible preservation of the visual field [10], and less myopia [13] in long-term observation are the arguments for anti-VEGF use. A still discussed issue is whether and to what extent anti-VEGF agents applied locally may affect the overall development of children [14–18]. Incomplete regression after anti-VEGF treatment can lead to the persistent avascular retina (PAR) with its possible consequences: late reactivation and retinal detachment from retinal breaks in the thinned avascular retina [19, 20]. Longer and more frequent follow-up recommended until 55 weeks PMA [21] is challenging when children get older and do not cooperate. On the other hand, a study by Rodriguez *et al.* [22] confirmed that peripheral vascular changes visible in fluorescein angiography of the eyes treated with bevacizumab do not preclude excellent visual acuity. Also, in our study group there were no late recurrences in the patients treated with anti-VEGF injections. Therefore, promising results, both anatomical and functional, and lack of solid proofs of anti-VEGF systemic adverse side effects make it a possible treatment option, if used carefully, especially for zone I ROP.

As the treatment methods change over time, there is a need for a prompt assessment of the functional outcomes as they decide about the success of treatment. However, the quantitative VA measurements are difficult to obtain in the youngest patients, especially in children under 4 years of age, and even more challenging in the group of preterm born children who may have other comorbidities. In infants and nonverbal children below the age of 2.5 years, Teller Acuity Cards based on preferential looking may estimate grating acuity [23, 24] – yet short concentration span and less interest in the cards than in the surroundings often make the examination unreliable. In normally developing children, in most cases, it is possible to examine VA with Lea optotype charts from 2.5 years of age (nonverbal children may identify the symbols by pointing to them on the lap card). In children unable to complete VA testing with standard tests fixation paddles may



IVR – intravitreal ranibizumab injection

Figure 2. Distribution of spherical equivalent refractive error among the 3 groups of patients. Each category is defined as follows: hyperopia (≥ +3.0 D); physiological hyperopia/emmetropia (+0.5 D to –0.5 D); myopia (≤–0.5 D)

be shown to evaluate the ability to fix and follow and to assess the distance at which the children respond to the stimuli. However, despite their practicality for diagnosis and treatment this test do not provide quantitative measurements of VA.

In our study, we confirmed that the vast majority of our patients (89.5%) could see as they fixed and followed the Heidi face paddle. This is an especially satisfactory result taking into consideration: treatment due to the most severe ROP type – APROP and zone I ROP; the lasting effects that preterm birth itself has on the developing visual system [25] and neurological deficits strongly associated with ROP [26]. In our group, two patients in whom visual reactions were doubtful had severe and irreversible brain damage.

In the group of older patients (> 2.5 years), the majority (5 of 9 patients) were tested with Lea optotypes shown on the LCD panel. Similarly to the ETROP study [4], most studies categorize VA as normal if it is better than or equal to 20/40 (logMAR 0.3). In our study, only 2 eyes of 2 patients had VA better than equal to logMAR 0.3. This is probably due to the young age of the patients: most studies report good reliability of recognition quantitative visual acuity tests (such as Lea optotypes) starting at age 40 months on average [27]. In our cohort, three patients tested with Lea optotypes were younger.

The number of patients who were unable to complete VA testing with standard methods (Teller Acuity Cards or Lea optotypes) is high (12 of 19 patients) in our cohort. This is probably due to both young mean corrected age of the study group and developmental delays and neurological impairments, common in preterm born children. In some patients, however, the VA was satisfactory. We hope that the VA results will improve with the age of patients.

Refractive errors were common in our study group, and the majority of patients (68.4%) required correction with glasses, mostly due to myopia. Myopia occurred in all three groups of patients. Many studies confirmed that laser-treated ROP patients have a high incidence of myopia or high myopia [28–30]. In our study 1 out of 3 eyes treated with LP

alone (Group I) was myopic. As far as refractive errors in the patients treated with anti-VEGF injections are concerned, a recent meta-analysis and systematic review of Tan *et al.* [31] showed that the treatment with IVB is associated with less myopia and astigmatism than laser treatment for infants with severe ROP. However, although less prevalent than in laser-treated eyes, IVB-treated eyes also develop myopia [31]. This could be noticed in our results: In Group II (IVR) and Group III (IVR + laser), the percentage of myopic eyes was very high, 69.2% and 77.8%, respectively. The percentage of myopic eyes was higher in the group with IVR and deferred laser, however, the insufficient number of eyes in each group did not allow for statistical analysis.

According to the literature up to 80% of children with a history of severe ROP develop strabismus during the first 6 years of life [32]. A significant number of patients had strabismus (31.6%) and nystagmus (31.6%) in our study.

CONCLUSIONS

The anatomic results of zone I ROP treatment in our medical center improved compared to previous years. This validates the careful use of anti-VEGF injections as a first-line treatment in zone I ROP. Functional results of the current study are satisfactory as the majority of patients could see. However, the objective quantitative measurement, especially in children below 2.5 years of age past zone I ROP treatment, is difficult. Refractive measurements revealed a high number of myopic eyes both in children treated with IVR alone and in those treated with IVR with deferred laser photocoagulation.

DISCLOSURE

The authors declare no conflict of interest.

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