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Aggressive treatment – against aggressive disease

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Background: The aim of the study was to present the anatomical outcomes of our new method for the treatment of aggressive posterior retinopathy of prematurity (APROP).

Materials and methods: The "triple procedure" proposed by us consists of 1) cryocoagulation in the anterior avascular zone, 2) diode laser photocoagulation applied anterior and posterior to the presumed ridge, 3) supplemental diode laser applications on the vascular nets up to the clear retina. The method was used in 58 eyes of 29 infants with Zone I retinopathy of prematurity (APROP) during 4 years (2002–2005) with at least 6 months of follow-up after treatment.

Results: Average number of laser spots were 1149.4 ± 447.7 per eye, average number of cryoapplications were 55.3 ± 14.4 per eye. In 98.3% (57 of 58) of eyes anatomical outcome was favourable. Proliferative tissue totally regressed in all but 1 eye (1.7%) which developed stage IVB Retinopathy of Prematurity.

Conclusion: Our proposed "triple procedure" enables unsurpassed positive outcomes in aggressive posterior ROP treatment.

Key words: retinopathy of prematurity (ROP), Zone I disease, aggressive posterior ROP, laser therapy, cryotherapy

INTRODUCTION

Retinopathy of prematurity (ROP) is a potentially blinding disease affecting the smallest and youngest members of society, causing extremely long years of blindness. Based on the worldwide statistical facts there are about 45 million blind people all over the world, of those around 3% are children (1). ROP accounts for the majority of blindness cases among children in both high and middle income countries. In the United States, ROP remains the second most common cause of childhood blindness (2).

The World Health Organization's "Vision 2020" program (3) evaluates ROP as an "avoidable disease". Early detection and proper treatment of the disease has to be the key for achievement of this purpose. As described in the "Vision 2020" program, recent research has resulted in strategies that have been successful in reducing the incidence of ROP. One of the most important segments in this chain of blindness prevention is the proper treatment of ROP. It is necessary to make the treatment modality as effective as possible and bringing the least harm to the baby.

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Screening for ROP in Lithuania was started in Vilnius University Children's Hospital in 1994. Because of the severe shortage of quality equipment and skilled staff all screening, treatment and postoperative follow-up procedures had to be carried out by the authors of this article. During 11 years, 360 infants reached threshold and underwent treatment.

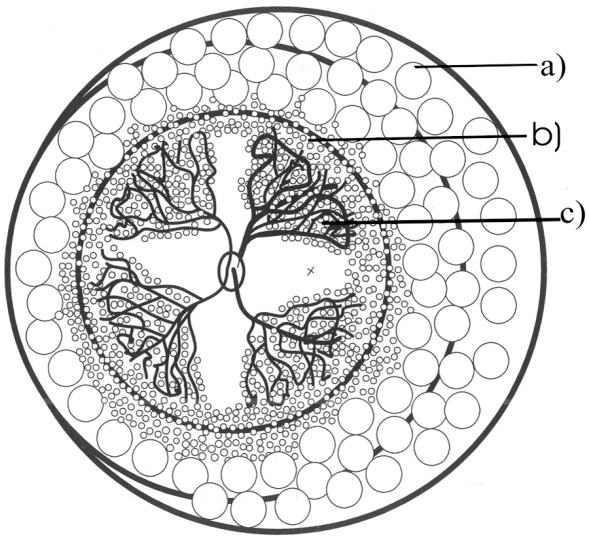

Fig. 1. Schematic drawing of the "triple procedure": a) cryo on anterior avascular retina; b) laser on both sides of the ridge; c) laser on vascular nets

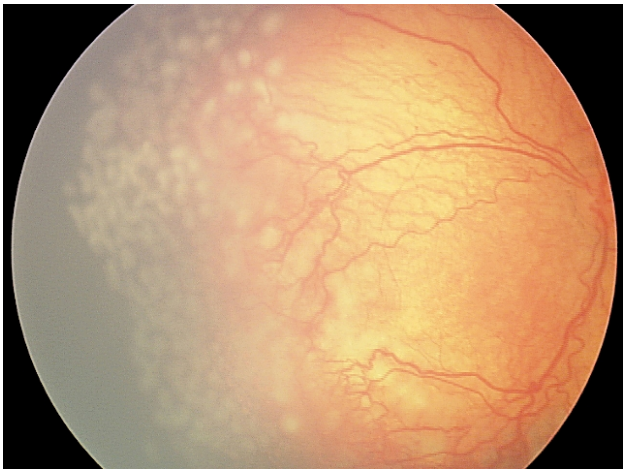

Fig. 2. Laser applications placed anterior and posterior (between the vessels) to the ridge

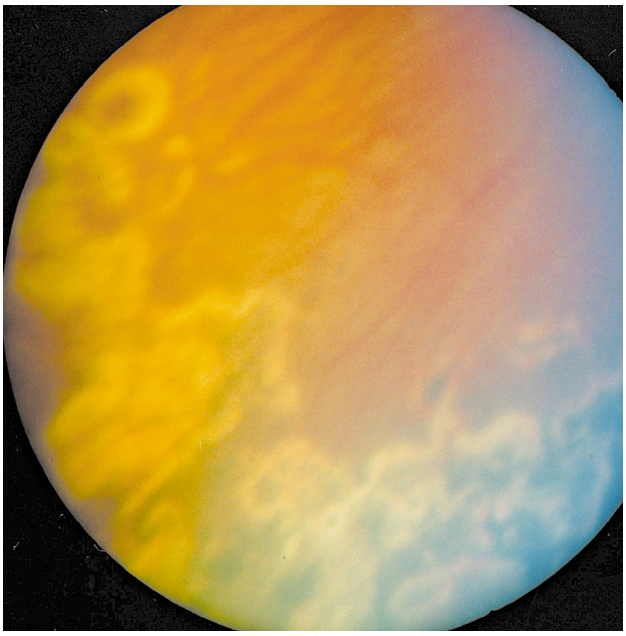

Fig. 4. Laser spots 3 months after the procedure

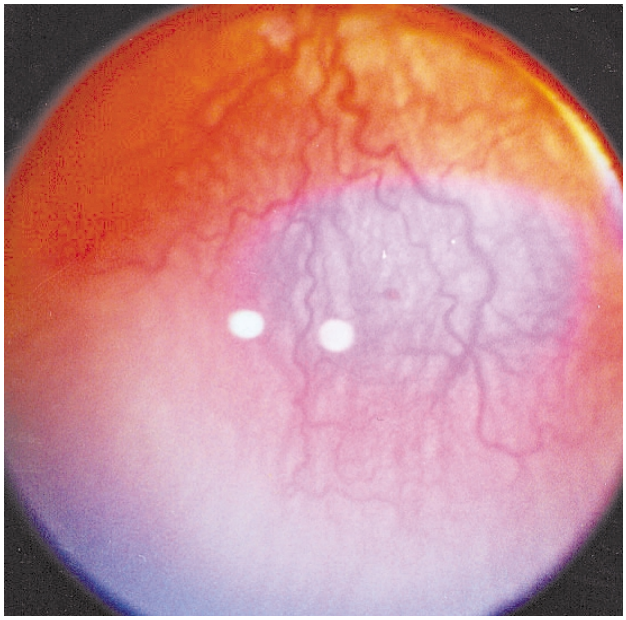

Fig. 3. Tiny vascular nets between the vessels in Zone I ROP

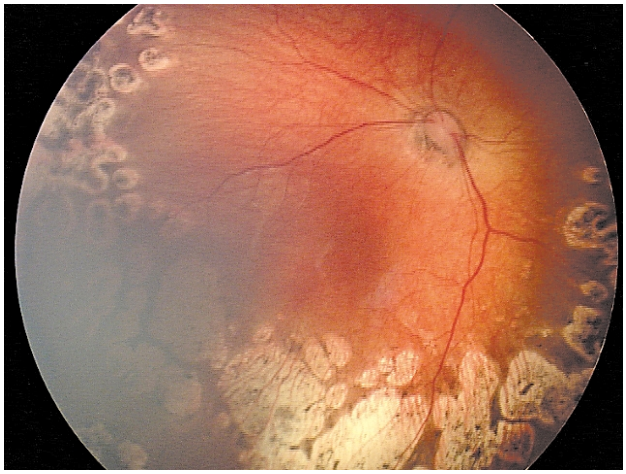

Fig. 5. Anatomical result 6 months after treatment: no proliferation, flat retina

Zone I threshold disease was diagnosed in 204 eyes (28.9%), and zone II threshold ROP was detected in 503 eyes (71.1%).

Absence of strict treatment modalities encouraged us to critically evaluate all recommendations and pick up the most beneficial elements from different presentations. Combination of those elements with our personal experience resulted in a new method of APROP treatment presented below.

The structural (anatomical) outcomes of the application of our new method during years 2002–2005 are presented in this paper.

MATERIALS AND METHODS

All consecutive premature infants hospitalized to Vilnius University Children's Hospital, who reached Zone I threshold ROP (APROP) were enrolled into the study. All

Table. **Results of treatment of APROP over the study period**

	2002	2003	2004	2005	Total
Success					
n of eyes (%)	13 (92.9)	22 (100)	8 (100)	14 (100)	57 (98.3.)
Failure					
n of eyes (%)	1 (7.1)	0 (0)	0 (0)	0 (0)	1 (1.7)
Total					
n of eyes	14	22	8	14	58

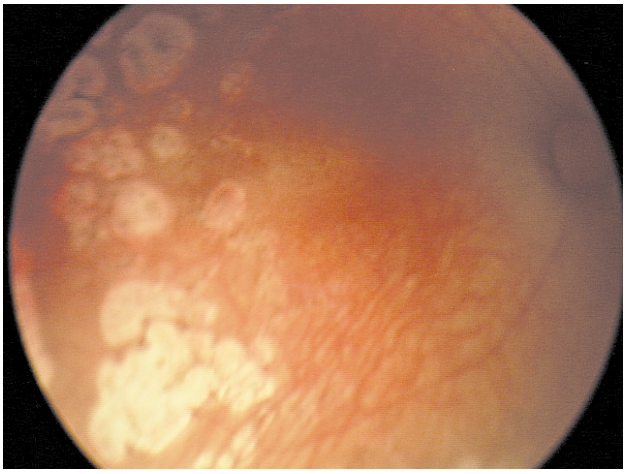

Fig. 6. Bare area of former ridge between laser spots

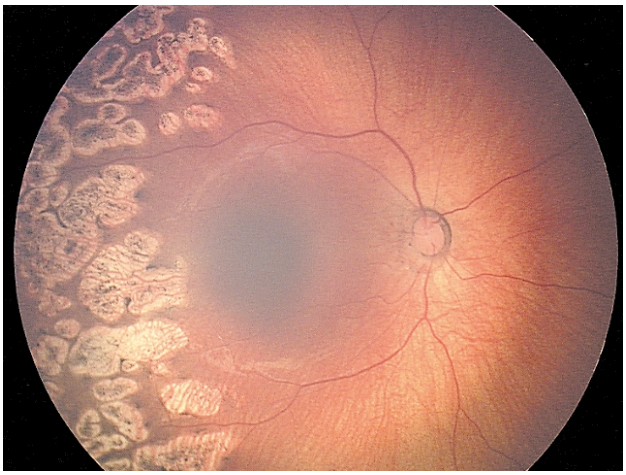

Fig. 7. Regressed proliferation, attached retina

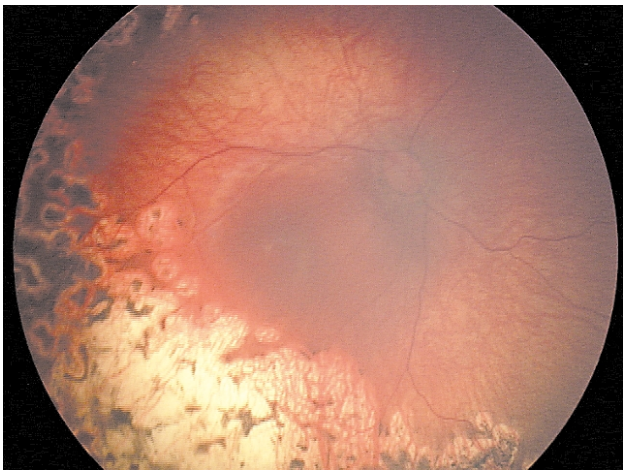

Fig. 8. Laser spots in close proximity to the macula

infants in this neonatal unit were outborn. They were referred from three Vilnius hospitals and some other hospitals from the whole Vilnius County. The study period confined January 2002 and December 2005. Threshold ROP was classified according to the CRYO-ROP Cooperative Group (4) of five or more contiguous or eight cumulative clock hours of stage 3 ROP in Zone I in the presence of "plus" disease. Marginal Zone I–II was not included into this study. These cases were ascribed to Zone II. The criteria for unfavourable outcome corresponded to those of CRYO-ROP study, including macular fold, retinal detachment, or retrolental fibroplasia (5). Treatment was administered within 24–48 hours after diagnosis. All procedures were conducted in the operating room using general anesthesia.

An 810 nm wavelength indirect diode laser ophthalmoscope (Iris Medical Inc., CA, USA) and cryoequipment (Erbe, Germany) were used for all procedures. The pupils were dilated with 0.5% Tropicamide drops. Maximum mydriasis was obtained with the use of 2.5% Neosynephrine, 1% Cyclopentholate or 0.1% Atropine solutions.

The whole peripheral avascular retina was treated by transconjunctival cryoaplications (Fig. 1).

In all cases we used the so-called "four-hand" technique originated by us (6); it enabled making the procedure quicker and safer, which is most important for the potentially bleeding eye.

By transpupillary indirect laser ophthalmoscope laser applications with an approximately half burn diameter between burns were performed in the bear retina anterior to the ridge (between the ridge and cryospots). The largest amount of laser applications was done posterior to the ridge (Fig. 2).

The ridge itself, if present, was not treated. In most cases there is no typical ridge in APROP (Fig. 3).

Tiny vascular nets with atypical location of proliferating tissue are the most common features of this disease (6, 7). The whole branched area was covered by several rows of laser spots. Laser spots were applied in close proximity to the macula, avoiding fovea and papillomacular bundle in the most severe cases (Fig. 1).

Ung. Tetracyclini or ung. Tobramycini were used at the end of the procedure. Postoperatively steroid drops were instilled four times a day and mydriatics were applied (two times a day) for 2–3 weeks. All infants were reexamined after the procedure in 6–10 days. Follow-up examinations were performed biweekly until disease regression (Fig. 4).

Assessment of the anatomical result was performed at least 6 months after treatment (Fig. 5).

The result remained stable after 3 and 6 months after therapy in all eyes.

RESULTS

During 2002–2005, a total of 29 neonates suffering from aggressive posterior ROP were treated by the treatment modality described above. The disease was bilateral in all cases. 58 eyes underwent treatment. Plus disease was present in all eyes. In our cohort all infants had 12 clock hours Zone I ROP.

Tunica vasculosa lentis (TVL) was present in 40 eyes. One eye had grade IV of TVL, 17 eyes had grade III, 18 eyes grade II and 4 eyes had grade I TVL.

The mean BW of Zone I threshold infants was 954.5 g (range: 685–1300 g, SD = 172.1 g). The Mean GA

was 26.7 weeks (range: 23–32 weeks, SD = 1.9 weeks).

The average number of laser spots was 1149.4 ± 447.7 per eye (range, 374–2148), the average number of cryoapplications being 55.3 ± 14.4 per eye.

The mean number of laser spots was 1173.8 ± 462.2 in the right eye and 1124.0 ± 439.8 in the left eye. The power level ranged from 200 mW to 800 mW, duration 0.2 seconds. The mean number of cryopapplications was 55.7 (range: 23–87, SD = 14.8) for the right eye and 54.8 (range: 26–80, SD = 14.3) for the left eye. The mean age at treatment was 34.7 weeks (range: 32–38, SD = 1.7).

Retreatment was performed for 4 eyes (two infants). The results of treatment of Zone I ROP for each year are presented in Table.

Finally, 57 retinas (98.3%) were flat without dragged vessels. The bare area of the former ridge was clearly seen (Fig. 6).

Proliferative tissue totally regressed (Fig. 7) in all but one eye (1.7%) which developed stage IVB ROP. Some of laser spots were in a very close proximity to the macula (Fig. 8), sometimes even in the lateral part surrounded by macular reflex.

DISCUSSION

In 1990, the Cryotherapy for Retinopathy of Prematurity Cooperative Group (CRYO-ROP CG) (8) announced a three-month outcome of Zone I ROP treatment. Favourable anatomical outcome was achieved in 25%, however, only 12 eyes were treated.

More recently, several studies have suggested that laser therapy is as effective as cryotherapy or sometimes even superior to cryotherapy in reducing unfavorable outcomes (9–12). But all authors unanimously emphasized that Zone I ROP showed the largest amount of unfavourable outcomes in their studies. For example, in 1993 Hunter and Repka reported regression of Zone I disease in three of four eyes treated with diode laser (11). A similar success rate was achieved by McNamara and coworkers (10) (disease regression in one of three eyes). Katz et al. (13) described results at three months after Zone I ROP treatment; 40% of eyes had an unfavourable outcome. In particular, we do not think that the number of laser spots was sufficient in this study. Shapiro et al. (14) emphasized that "consideration of the treatment by modality revealed failure in four of five (80%) eyes with cryotherapy and five of 20 (25%) eyes with photocoagulation". We totally agree with these authors' assertions that treatment with cryotherapy may be particularly problematic in Zone I disease.

At the same time, very rare proposals about treatment posterior to the ridge were heard. For example, Nomura et al. (15) used 2–3 lines of laser applications posterior to the ridge. A similar technique with an additional row of the laser burns added posterior to the ridge was described by Axer-Siegel et al. (16). Of the 18 eyes that received laser treatment to the vascular retina posterior to the ridge two developed retinal detachment. Capone et al. (17) described a favourable outcome in 83.3% of 30 eyes with Zone I ROP that were treated with diode laser.

Our personal 11-year experience in screening, treatment and postoperative follow-up of infants with ROP made it possible to introduce modified treatment modalities and to achieve better results. Our success rate in the treatment of Zone I ROP, even wthen treatment was not so aggressive, considerably exceeds the results of previous publications (18, 19). Our efforts to find any study describing treatment of Zone I ROP with a number of eyes greater than ours and an outcome exceeding ours were unsuccessful.

According to our results, during 2002–2005 years no one infant with Zone I ROP became bilaterally blind. After introduction of the "triple procedure" we failed in one eye. Even considering our success rate (92.9%, with one failure case in 2002), our worst result exceeded the highest percentage of the published data.

None of the previously available treatment modalities allowed achieving such a high percentage of favourable outcomes.

Somebody can argue with us concerning the severity of the disease. We are sure about the proper diagnosis, because all our analysis is formed on a set of cases which exclude marginal Zone I–II cases of ROP. There even were cases in which the anterior border of the vessels was posterior to the macula. We have never seen Zone I ROP extending less than 12 hours. However, there are different misleading features of Zone I disease. Neovascularisation does not follow the usual progression of this condition from stage 1 to stage 3 (6, 7). The International Classification of ROP is not suitable for determination of stages of Zone I ROP. The ridge is almost always not evident, but the vessels come and the proliferation starts not avascularly but along the main vessels and even crossing the optic disk. Only continual observation of the development of the disease could lead to a better understanding and management of the disaster.

When applying laser we usually tried to put spots near the vessels, but not only circularly in vascular retina. In the most severe cases laser applications were applied in one or even less than one disk diameter apart from the optic disk corresponding to the layout of branching blood vessels. All such cases treated by other modalities used to fail in our previous practice.

We think that these tiny nets of vessels of the shunting area in Zone I ROP produce the vascular endothelial growth factor (VEGF), and this area must be excluded in any treatment modality. Therefore laser applications must be applied to the clear retina between the vessels. In our opinion, aggressive posterior laser therapy was the key to our success. We would like to share our experience regarding the priorities of our treatment modality. First of all, if there is a true Zone I ROP, it demands a huge amount of laser spots to cover the whole avascular retina.

For example, Lambert et al. (20) describe the treatments when they used 4000 and even more applications. This treatment was complicated by cataract, phthisis bulbi. On the other hand, we do not believe that 1000 or 1500 spots are enough in such severe cases for covering the entire avascular fundus.

Secondly, tunica vasculosa lentis (TVL) is often obscuring the view of the fundus and impeding the procedure. In such cases it is especially difficult for a laser beam to reach the anterior parts of the fundus, and, in our opinion, cryotherapy is extremely helpful in such eyes. By the way, the most severe cases have the most distinct TVL (21).

Thirdly, covering the peripheral fundus with cryo spots allows us to save the time of the procedure, because one cryo spot is approximately 20 times bigger than a laser spot.

Fourthly, arguing with those who declare that myopic refraction is higher in cryotreated eyes (22), we think that the favourable anatomical outcome in Zone I ROP is much superior to eventual development of blindness.

Fifthly, randomized clinical trials would be beneficial, but even the slightest possibility of blindness caused by such trials would be too high a price for a scientific research. Even multicenter CRYO-ROP trials were not completed when it became evident that the benefits of that particular treatment exceed the harm of the disease (4, 8).

CONCLUSIONS

1. The “triple procedure” proposed by us enables unsurpassed positive outcomes in zone I ROP treatment.

2. To our knowledge, this is the largest series of successful Zone I ROP treatment reported.

3. On the basis of our findings this treatment modality could be recommended for practical use.

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