

Retinopathy of prematurity: modified treatment modality for Zone II disease

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Introduction: Retinopathy of prematurity is a disease of prevention, and a timely and proper treatment is the key to success in the fight against this disaster. This is the first report worldwide of such favorable multi-year results in consecutive 390 treated eyes.

Purpose: In this paper we present our unique modified cryotherapy modality for Zone II ROP treatment which enables complete prevention of blindness caused by this kind of disease.

Materials and methods: Out of 2159 infants screened for ROP in Vilnius University Children's Hospital from January 1995 to December 2003, threshold ROP was diagnosed in 320 infants (14.8%). Of them, 182 eyes had Zone I ROP, and for 445 eyes Zone II ROP was diagnosed. Every Zone II ROP threshold infant underwent cryotherapy. All screening, treatment and postoperative follow-up procedures were performed by the same two ophthalmologists (RB and RS).

Our modified cryotherapy consisted of two rows of cryoapplications: one row on the ridge and the other row anterior to the ridge. Not the whole area of the anterior avascular retina up to ora serrata was covered by cryoapplications.

Results: 55 eyes were treated by traditional cryotherapy through 1995. Modified cryotherapy was applied in 390 eyes with Zone II ROP from 1996 to 2003.

Favorable results were obtained in 52 eyes (94.5%) treated by traditional cryotherapy. Our modified cryotherapy was successful in all 390 eyes (100%).

Conclusion: Our multiyear hands-on personal experience with the above-mentioned modality clearly shows that blindness caused by Zone II ROP can be completely prevented.

Key words: retinopathy of prematurity (ROP), cryotherapy, Zone II disease

INTRODUCTION

Retinopathy of prematurity (ROP) is a disease of prevention, and a timely and proper treatment is the key to success in the fight against this disaster. In the ninth decade of the last century, cryotherapy was started to use for ROP treatment. This method gained the widest acceptance after Cryotherapy for Retinopathy of Prematurity Cooperative Group (CRYO ROP CG) had published their results (1) and it became

evident that this treatment methodology would allow for prevention of many children blindness cases. At the turn of the century, another treatment form – lasertherapy – gained a substantially wider application for treatment of the disease, especially in the western countries (2). It was being stated that lasertherapy resulted in less complications, and provided blindness prevention as effective as cryotherapy. Over the years there has been a consistent improvement using both therapy modalities, but none of them resulted in a 100% success rate. However, the total cost of required equipment for lasertherapy is much higher than for cryotherapy, and this factor is essential for the poor developing countries of the world, where the epidemic wave of ROP is just starting.

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In this paper, we present our unique modified cryotherapy modality for Zone II ROP treatment, which enables a complete prevention of blindness caused by this kind of disease.

MATERIALS AND METHODS

2159 infants were screened for ROP in Vilnius University Children Hospital from January 1995 to December 2003. All these infants were outborn. Threshold ROP was diagnosed in 320 infants (14.8%). Of them, 182 eyes had Zone I ROP, and for 445 eyes Zone II ROP was diagnosed. All Zone II ROP (Fig. 1) threshold infants underwent cryotherapy. One infant died during operation because of multiple congenital malformations and was excluded from result evaluation. All screening, treatment and postoperative follow-up procedures were performed by the same two ophthalmologists (RB and RS). All infants had their threshold status confirmed by both examiners. The presence of retinopathy and indications for treatment were in accordance with International Classification of ROP and CRYO ROP CG (3, 1). Posterior Zone II cases were ascribed to Zone II. The criteria for unfavorable outcome corresponded to those of CRYO ROP CG study, including macular fold, retinal detachment, or retrolental fibroplasia (1, 3). Treatment was administered within 24–48 hours after diagnosis. Cryotherapy was always carried out in the operating room using general anesthesia.

Cryoequipment (Erbe, Germany) with a cataract probe and binocular indirect ophthalmoscope (Keeler) with +20 and/or +28 D lenses were used for all procedures (4). The pupils were dilated by 0.5% Tropicamide drops. Maximum mydriasis was obtained with additional use of 2.5% Neosynephrine, 1% Cyclopentolate or 0.1% Atropine solutions. Ung. Tetracyclini or ungu. Tobramycini were used at the end of the procedure. Postoperatively, steroid drops were instilled four times a day and mydriatics were applied (2 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. The second or third treatment procedure (if necessary) was performed within 10–14 days after the previous one.

The structural (anatomical) outcome was evaluated in treated infants at least 6 months after the procedure.

The traditional (recommended by CRYO ROP CG) modality – treatment anterior to the ridge (Fig. 2) – was used in 1995. Our modified cryotherapy consisted of two rows of cryoapplications: one row on the ridge and the other row anterior to the ridge. Not the whole area of the anterior avascular retina up to ora serrata was covered by cryoapplications (Fig. 3). This kind of treatment has been applied in eyes with Zone II ROP from 1996 (5, 6).

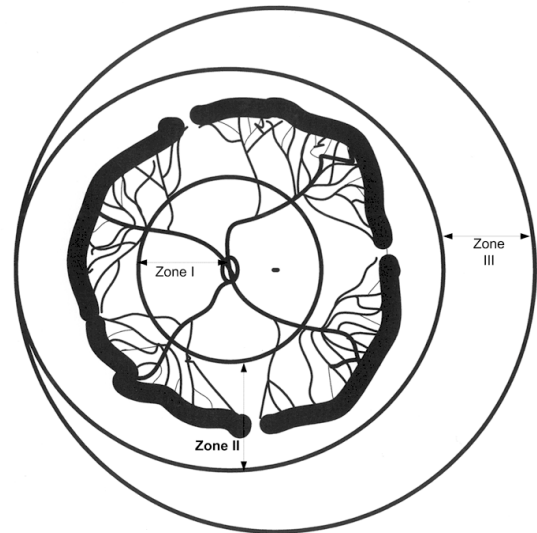


Fig. 1. Retinopathy of prematurity: Zone II disease

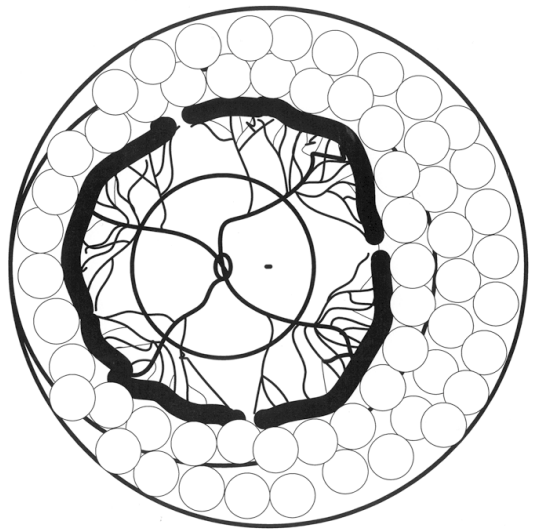


Fig. 2. Traditional cryotherapy of all avascular retina

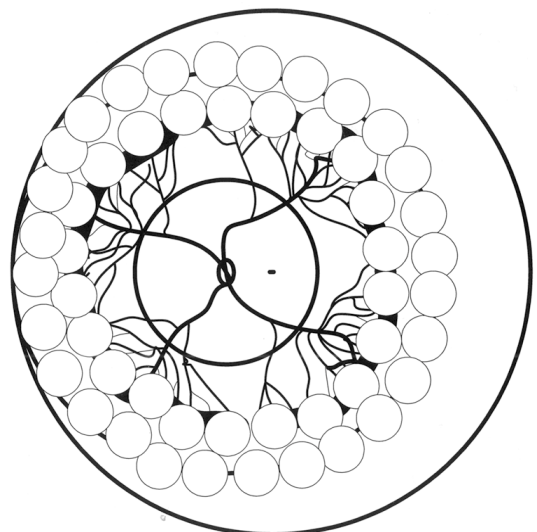


Fig. 3. Our modified cryotherapy. Two rows of cryoapplications: one row on the ridge and the other row anterior to the ridge

In order to make cryotherapy as effective as possible and as harmless as possible for the baby, we have introduced a few additional improvements of the cryoprocure from the very beginning of our work:

1. The so-called "four hands technique". The cryotherapy procedure is performed by two physicians. The first one performs ophthalmoscopy holding a lens in one hand and drops BSS solution onto the eye during the thaw period. The second physician, using a cryoprobe, indents the exact place, and with a gentle manipulation with a strabismus hook in the other hand brings the avascular zone into view, or regulates the position of the lid speculum.

2. Small gauze is placed between the eyelid and the cryoprobe to prevent the eyelid from freezing.

3. Dropping of a balanced salt solution on the cornea and cryoprobe after every cryoapplication allows for shortening the unfreezing period and prevents the eyelid and corneal damage.

RESULTS

Using the traditional cryotherapy recommended by CRYO ROP CG, adverse outcome was diagnosed in 3 eyes. Favorable results were obtained in 52 eyes (94.5%). Modified cryotherapy was successful in 390 eyes (Table 1).

None of the eyes needed more than two treatments in modified cryotherapy (Table 2). All eyes that needed the second procedure in the modified cryotherapy group belonged to posterior Zone II. Also, skipped areas observed on follow-up near the ridge were treated.

Small ridge hemorrhages without sequela for outcome were observed in 18.2% (10/55) of eyes treated by traditional cryotherapy and in 11.8% (46/390) of eyes treated by modified cryotherapy. None of the complications described in CRYO ROP CG study, such as tumor like conjunctival hemorrhages and unintended conjunctival lesion, were observed in our study cohort.

DISCUSSION

Yamashita from Japan was the first to announce positive results of transconjunctival cryotherapy (7). Since the very beginning of cryotherapy for ROP there were ideas on two possible treatment modalities: treatment on the ridge and treatment of avascular retina (8). Our modified cryotherapy resembles the treatment modality described in the eighties (8). The CRYO ROP CG study recommended avoiding the ridge because of severe complications (1). Our improvements enable prevention of those complications.

The main drawback of our modality is that two persons perform the procedure instead of one as described in CRYO ROP CG, however, we believe this pays off for the sake of baby's vision.

It is rather difficult to manipulate with a cryoprobe in one hand, especially when the disease is located posterior to the equator. For a better visualization of indented retina it is necessary to rotate the globe and to use a higher pressure on the globe. These factors may cause insufficient blood supply or hemorrhages. In addition, it is impossible to protect the eyelids from freezing when the procedure is performed by one surgeon. Besides that, someone else has to drop solution on the cryoprobe at the end of the freezing. This maneuver enables prevention of excessive eyelid freezing and shortens the thawing of the ice ball. Such a simple improvement shortens the whole treatment procedure to a considerable extent, which is extremely important for a sick and small baby.

To summarize, the benefit of all improvements allowed a more proper localization of cryoapplications and a less pressure on the eye, which enabled to minimize the risk of retinal, subretinal, or intravitreal hemorrhages, caused less disturbances of the retinal blood flow, lowered the risk of globe perforation by the cryoprobe the hazard for infant's heart vital activity.

We had a unique opportunity to screen, treat and follow-up all infants personally. This was the main

Table 1. Results of treatment of Zone II threshold ROP

Year	1995	1996	1997	1998	1999	2000	2001	2002	2003
Success, number of eyes	52	67	71	48	62	32	27	33	50
Failure, number of eyes	3	0	0	0	0	0	0	0	0

Table 2. Frequency of procedures over the study period

Method of therapy	Traditional (1995)	Modified (1996–2003)
Single procedure, number of eyes (%)	40 (72.7)	368 (94.4)
Second procedure, number of eyes (%)	9 (16.4)	22 (5.6)
Third procedure, number of eyes (%)	6 (10.9)	0 (0.0)
Total number of eyes (%)	55 (100%)	390 (100%)

difference from multicenter trials: the CRYO ROP CG study enrolled 23 centers (1), STOP ROP (9) enrolled 30 centers, ET ROP (10) – 26 centers. In our study cohort, the total number of treated eyes was 445, *i.e.* closely approached the numbers of eyes investigated in the centers mentioned above. This is a sufficient number for making comparisons and for summarizing our experience. In the ET ROP study, treatment was applied for 597 eyes, in the CRYO ROP study 172 infants underwent therapy. When we used the modality recommended by the CRYO ROP study at the very beginning of our work in 1995, our results were similar to those obtained in that study. During that period we had much more infants requiring repeated therapy: 16.4% were treated twice and 10.9% were treated three times. We believe that the improvements of cryoprocure described above allowed us to reduce the amount of complications in comparison to the CRYO ROP study.

The main reason that lead us to modified cryotherapy was an accidental application of cryo spots on the ridge. Only the places with cryospots on the ridge were free of proliferating tissue in unfavorable eyes. This encouraged us to change the treatment modality. The unbelievable rate of success did not allow us to turn back to the traditional modality. We were not restricted by any treatment protocols, because in the former soviet system ROP was an unknown disease and in the newly founded independent national health care system such protocols have not yet been created.

Only 5.6% of the eyes were retreated, with favorable results, in the modified cryotherapy group. The total success rate (structural outcome) was 100% during 1996–2003. There are many papers from different countries about their results on ROP treatment. In a study from Belgium (11), retinal detachment occurred within one month after cryotherapy in 10 eyes of 58 patients. As Azad et al. (12) from India describe, an overall unfavorable outcome occurred in 17.07% of 50 children treated for threshold ROP. McGregor et al. from Columbus, Ohio (2) used two modalities of ROP treatment, laser and cryotherapy, for 100 consecutive infants. His conclusion: no statistically significant difference was found in the rate of retinal detachments in the two groups.

All authors unanimously declare that outcomes in Zone II ROP are much better than in Zone I, but very few (13, 14) present such high success rates. Results published by those authors are based on a relatively small number of treated eyes; meanwhile we have a much broader result set.

This kind of treatment will be denied by those who perform laser therapy. We do agree that laser ablation is superior to cryotherapy of avascular retina, but for us the success rate of 100% is the main motivation. Improvements of surgical techniques al-

lowed us to reduce the number of complications to minimum. On the other hand, some devastating complications are described in laser therapy such as cataract (2, 15, 16), phthisis (15), vitreous hemorrhage, posterior synechia, macular ectopia (16). Furthermore, modified cryotherapy is extremely favorable in cases where fundus visualization is severely obstructed by tunica vasculosa lentis and a poorly dilated and vascularized pupil.

Randomized trials would be beneficial for more proper investigations, but the amount of treated eyes, personal experience during the course of disease, and the 100% success rate in cryotherapy for Zone II ROP in 390 eyes is superior to even one blind eye for the sake of scientific investigation. Moreover, nowadays cryotherapy is more easily acceptable in many developing countries to which the delayed wave of ROP is just coming.

Finally, we would like to note that our multiyear hands-on personal experience with the above-mentioned modality clearly shows that blindness caused by Zone II ROP can be completely prevented.

References

1. Cryotherapy for retinopathy of prematurity cooperative group. Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. *Arch Ophthalmol* 1988; 106: 471–9.
2. McGregor ML, Wherley AJ, Fellows RR, Bremer DL, Rogers GL, Letson AD. A comparison of cryotherapy *Versus* diode laser retinopexy in 100 consecutive infants treated for threshold retinopathy of prematurity. *J AAPOS* 1998; 2: 360–4.
3. The Committee for the Classification of Retinopathy of Prematurity. An International Classification of Retinopathy of Prematurity II. The classification of retinal detachment. *Arch Ophthalmol* 1987; 105: 906–12.
4. Bagdoniene R, Sirtautiene R. Treatment of ROP. In: Bagdoniene R, Sirtautiene R, eds. *Neišnėdiotø naujagimjø retinopatija / Retinopathy of Prematurity*. Vilnius; Gilija. 1998: 28–9, 93.
5. Bagdoniene R, Sirtautiene R. Cryotherapy for ROP. A two-year experience. In: Suveges I, Follmann P, eds. *SOE '97. XIth Congress of the European Society of Ophthalmology*. Bologna; Monduzzi Editore. 1997: 967–71.
6. Bagdoniene R, Sirtautiene R. Threshold retinopathy of prematurity in Lithuania. Tendencies during three years. In: Reibaldi A, Di Pietro M, Scuderi A, Melerba E., eds. *Progress in Retinopathy of Prematurity. Proceedings of the International Symposium on Retinopathy of Prematurity*, Taormina. Amsterdam / New York; Kugler Publications. 1997: 31–6.
7. Yamashita Y. Studies on retinopathy of prematurity III. Cryotherapy for retinopathy of prematurity. *Jpn J Clin Ophthalmol* 1972; 26: 385–93.

8. Hindle NW. Location and Timing of Intervention with Cryotherapy. In: McPherson AR, Hittner HM, Kretzer FL, eds. Retinopathy of Prematurity. Current Concepts and Controversies. Toronto Philadelphia; BC Decker Inc. 1986: 143–9.
9. The STOP-ROP Multicenter Study Group. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP). A randomized, controlled trial I: Primary outcomes. Pediatrics 2000; 105: 295–310.
10. Early Treatment for retinopathy of prematurity cooperative group. Revised Indications for the treatment of retinopathy of prematurity. Arch Ophthalmol 2003; 121: 1684–96.
11. Casteels I, Verdonk N, Allegaert K, Naulaers G, Devlieger H. Structural and functional outcome in infants treated with cryotherapy for threshold retinopathy between 1989 and 1999. J Pediatr Ophthalmol Strabismus 2003; 40: 75–80.
12. Azad RV, Sethi A, Kumar H. Management outcome in prethreshold retinopathy of prematurity. J Pediatr Ophthalmol Strabismus 2003; 40: 330–4.
13. Kim RW, Rezai KA, Elkhaimi MA, Elliott D. Near confluent panretinal photocoagulation for the treatment of threshold retinopathy of prematurity. Invest Ophthalmol Vis Sci 2002; 43: e-Abstract 1246.
14. Rosenberg KD, Murray TG, Berrocal A, Ysasaga E, Loo R, Aragon A et al. Continuous *versus* non-continuous laser photocoagulation for the treatment of threshold retinopathy of prematurity. Invest Ophthalmol Vis Sci 2003; 44: E- Abstract 596.
15. Lambert RS, Capone Jr A, Cingle KA, Drack AV. Cataract and phthisis bulbi after laser photoablation for threshold retinopathy of prematurity. Am J Ophthalmol 2000; 129(5): 585–91.
16. Fallaha N, Lynn MJ, Aaberg TM Jr, Lambert SR. Clinical outcome of confluent laser photoablation for retinopathy of prematurity. J AAPOS 2002; 6: 81–5.

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NEIÐNEÐIOTØ NAUJAGIMIØ RETINOPATIJA: MODIFIKUOTAS ANTROSIOS ZONOS LIGOS GYDYMO BÛDAS

S a n t r a u k a

Neiðneðiotø naujagimiø retinopatija – tai liga, kurios iðvengtø padëtø tinkamas ir savalaikis gydymas. Ðiame darbe pirmà kartà pasaulinëje praktikoje pristatomas modifikuotas gydymo metodas, sèkmingai taikytas 390 akiø, gydytø dël neiðneðiotø naujagimiø retinopatijos antrosios zonos ligos.

Tikslas. Pateikti Ðio straipsnio autoriø rekomenduojamà modifikuotà krioterapijos bûdà antrosios zonos neiðneðiotø naujagimiø retinopatijai gydyti.

Tyrimo medþiaga ir metodai. Nuo 1995 metø sausio mënësio iki 2003 metø gruodþio mënësio Respublikinëje Vilniaus universitetinëje ligoninëje 2159 neiðneðiotø naujagimiai buvo tirti dël retinopatijos. Slenkstinë neiðneðiotø naujagimiø retinopatija diagnozuota 320 (14,8%) vaikø. Pirmosios zonos retinopatija stebëta 182 akyse, o antrosios zonos – 445 akyse. Visiems kûdikiams, sirgusiems antrosios zonos retinopatija, buvo atlikta krioterapija. Ðio straipsnio autorës paëios atrinko kûdikius, gydë ir stebëjo juos po operacijos.

Rezultatai. Tradicine krioterapija gydytos 55 akys pirmaisiais darbo metais, o 1996–2003 metais modifikuota krioterapija buvo atlikta 390 akiø. Autoriø pasiûlytos krioterapijos esmë – atliekamos dvi krioaplikacijø eilës: viena – keteros srityje, kita – á priekà nuo keteros, taëiau gydoma ne visa avaskulinë tinklainë iki dantytosios linijos. Po tradicinës krioterapijos pasveiko 52 akys (94,5%), po modifikuotos krioterapijos – 390 akiø (100%).

Iðvada. Naudojant mûsø ilgamete praktine patirtimi patvirtintà modifikuotà gydymà Ðalëiu, galima visiðkai iðvengti aklumo dël antrosios zonos neiðneðiotø naujagimiø retinopatijos.

Raktaþodþiai: Neiðneðiotø naujagimiø retinopatija (NNR), krioterapija, antrosios zonos liga