·Clinical Research·

Late clinical characteristics of infants with retinopathy of prematurity and treated with cryotherapy

Eren Cerman[1], Deniz Ozarslan Ozcan[2], Hande Celiker[1], Muhsin Eraslan[1], Ozlem Sahin[1], Haluk Kazokoglu[1]

[1]Department of Ophthalmology, Marmara University School of Medicine, Istanbul 34890, Turkey
[2]Department of Ophthalmology, Akcakale State Hospital, Sanliurfa 63500, Turkey
Correspondence to: Eren Cerman. Department of Ophthalmology, Marmara University School of Medicine, Istanbul 34890, Turkey. erencerman@yahoo.com
Received: 2015-01-27 Accepted: 2015-05-20

Abstract

• AIM: To describe the clinical characteristics and late results of patients with retinopathy of prematurity (ROP) treated with "6h cryotherapy".

• METHODS: Out of 1252 infants screened for ROP, 52 patients were treated with temporal 6h cryotherapy from 1997 to 2005 were recalled to our clinic. Among these 23 patients were available and 46 eyes of 23 infants were included to evaluate for visual acuity, refractive error, ocular alignment, nystagmus, retinal examination (abnormal branching of retinal vessels, retinal thinning, latis degenerations, tortuosity of vessels, straightening of temporal vessels, narrowing of the angle of vessel in the juxtapapillary entrance, pigment changes, macular heterotopia), optic atrophy and optic disc cupping, axial length at birth and axial length at 1y.

• RESULTS: The median age at examination was 7 (5-18)y. In 32.6% of patients, the visual acuity was ≤20/200 and the mean best corrected visual acuity was 20/35 as measured with a Snellen chart. Mean spherical refractive error was -1.76±2.69 D. The degree of myopia at the last examination was found to be correlated with the elongation of the eye in the first year of life. Exotropia was present in 17.4% (*n*=8) of infants and esotropia in 13% (*n*=6). The most common retinal abnormality was abnormal branching of retinal vessels (82.6%) followed by retinal thinning (52.2%).

• CONCLUSION: The late clinical outcomes of infants with ROP treated in our clinic with cryotherapy seems to comparable with results of laser treatment.

• KEYWRODS: retinopathy of prematurity; cryotherapy; late outcomes

DOI:10.18240/ijo.2016.04.15

Cerman E, Ozarslan Ozcan D, Celiker H, Eraslan M, Sahin O, Kazokoglu H. Late clinical characteristics of infants with retinopathy of prematurity and treated with cryotherapy. *Int J Ophthalmol* 2016;9(4):567-571

INTRODUCTION

Retinopathy of prematurity (ROP) is a retinal vascular disease affecting more than half of infants born before 28wk of gestation and is one of the most common causes of preventable blindness in childhood [1-2]. The cryotherapy for retinopathy of prematurity (CRYO-ROP) study established a marked reduction in unfavourable outcomes in eyes with threshold ROP from 47% in untreated eyes to 25% in eyes with ablation of the avascular retina with cryotherapy [3]. During the 1990s the use of laser photocoagulation for retinopathy has become an alternative[4-5]. In some of the first studies laser was reported to be likely to produce cataracts[6-8]. After some studies reported better visual and structural outcomes and reduced postoperative inflammation with laser treatment compared with cryotherapy [9-10]. The standard treatment modality for ROP in developed countries has become the laser treatment [11]. Currently in less developed countries access to cryotherapy compared to laser is greater[12]. In our clinic, cryotherapy was used until a laser photocoagulator was obtained, and in this study we report the late structural outcomes of 23 cases treated with cryotherapy for threshold disease and discuss the results in the light of literature.

SUBJECTS AND METHODS

In our clinic, cryotherapy was used until indirect laser photocoagulation device was obtained. In all cases cryotherapy was applied 6h temporally and not 360 degree. Among the patients who were screened in our center (*n*=1252) 52 patients who had threshold disease underwent cryotherapy treatment for ROP [13-14]. Patients who had plus (+++) disease and threshold disease in zone Ⅰ were not found clinically suitable for cryotherapy, because the cryo-lesion could extend to posterior retina, and were referred to a center where laser photocoagulation was available. The axial length was measured with an ultrasonic biometry device (Alcon, Occuscan RxP) and sciascopy was performed to measure

Table 1 The findings at first year and at last examination of infants treated with temporal 6 o'clock cryotherapy

Parameters	Mean	SD	Median	Min	Max
Findings at infancy					
Birth week (wk)	29.21	2.19	30	25	33
Birth weight (g)	1255	274	1200	880	1730
Axial length at birth (mm)	18.64	0.08	18.60	18.56	18.98
Axial length at first year (mm)	20.72	0.94	20.88	18.62	22.38
Axial elongation at first year (mm)	2.07	0.92	2.21	-0.07	3.81
Late findings					
Age at examination (a)	7.65	3.07	7	5	18
Spherical equivalent of refraction (D)	-1.76	2.69	-1.13	-8.00	+3.00
CDVA (Snellen)	0.57	0.44	0.80	LP	1.00

SD: Standart deviation; CDVA: Corrected distance visual acuity; LP: Light perception.

refractive error. All other patients treated with cryotherapy disease from 1997 to 2005 were recalled for a full ophthalmological examination.

The study was conducted in accordance with the principles in the Declaration of Helsinki. Before starting study, Marmara University School of Medicine Research Ethics Committee Approval Evaluation Commission (dated 06.20.2014 No. 09.2014.0158 protocol) were included. All patients or their parents provided informed consent before enrolment in the study.

Corrected distance visual acuity (CDVA) was determined using a Snellen chart, tumbling E or picture chart. Nystagmus was tested when children were fully awake. Nystagmus without occlusion was recorded as manifest, and nystagmus with one eye occluded was recorded as latent nystagmus. All retinal examination was done only by one of the authors. In fundus examinations, the patients were evaluated for abnormal branching of retinal vessels, retinal thinning, latis degenerations, tortuosity of vessels, straightening of temporal vessels, narrowing of the angle of vessel in the juxtapapillary entrance, pigment changes, macular heterotopia, visual acuity, nystagmus, optic atrophy and optic disc cupping.

For statistical analysis SPSS (Statistics for Windows, Version 17.0.SPSS Inc. Chicago, USA) and for curve fitting the trial version of Curveexpert 1.4 was used.

RESULTS

Among 1252 infants screened for ROP, 52 had been treated with cryotherapy. All were recalled to our clinic. The percentage of loss of follow up after treatment was 56% (n=29).

The remaining 23 infants that were included in this study, whom cryotherapy was perforemed in all patients bilaterally. In none of the patients progression of the disease after treatment or late detachment was seen. There were 13 female and 10 male patients whose median age at time of follow-up was 7 (5-18)y. The total cohort had a median birth week of 30 (25-33) and a median birth weight of 1200 (880-1730) g.

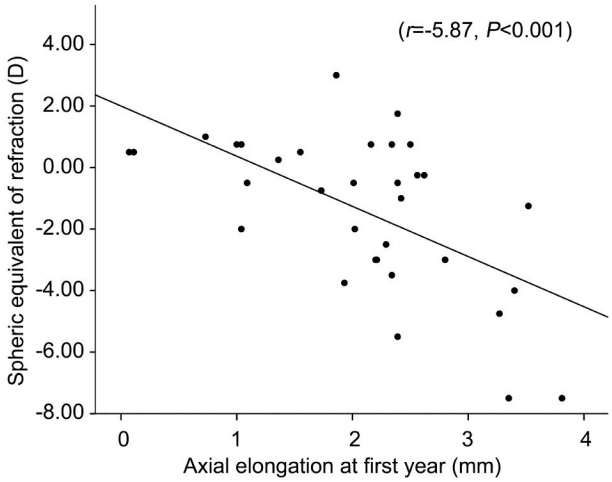

Figure 1 Correlation between the median axial elongation in the first year and the spherical refractive error at late clinical examination.

When the 46 eyes of the 23 patients were investigated, the overall mean CDVA was 20/35, where 69.6% of the eyes (n=32) CDVA was better than 20/200 and 58.7% (n=27) were between 20/40 and 20/20. Five children were diagnosed as having neurologic development deficits, and in these patients CDVA was lower than 20/200. The mean spherical refractive error was -1.76 (-8.00 to 3.00) D (Table 1).

In 37 of 46 eyes the axial length at first examination was recorded and the median axial length was found to be 18.60 (18.56-18.98), whereas in 33 of the eyes the median axial length at 1y was 20.88 (18.62-22.38) mm. The median axial elongation in the first year was 2.21, and in these 33 eyes the spherical refractive error at late clinical examination correlated reversely with axial elongation at first year (r=-5.87, P<0.001) (Figure 1).

Ocular movement examination revealed that 17.4% of infants had esotropia (n=8) and 13% had exotropia (n=6).

The most common observed retinal abnormality was abnormal branching of retinal vessels (82.6%, n=38) followed by retinal thinning (52.2%, n=24). Retinal vessel tortuosity was observable in 34.8% of the eyes (n=16).

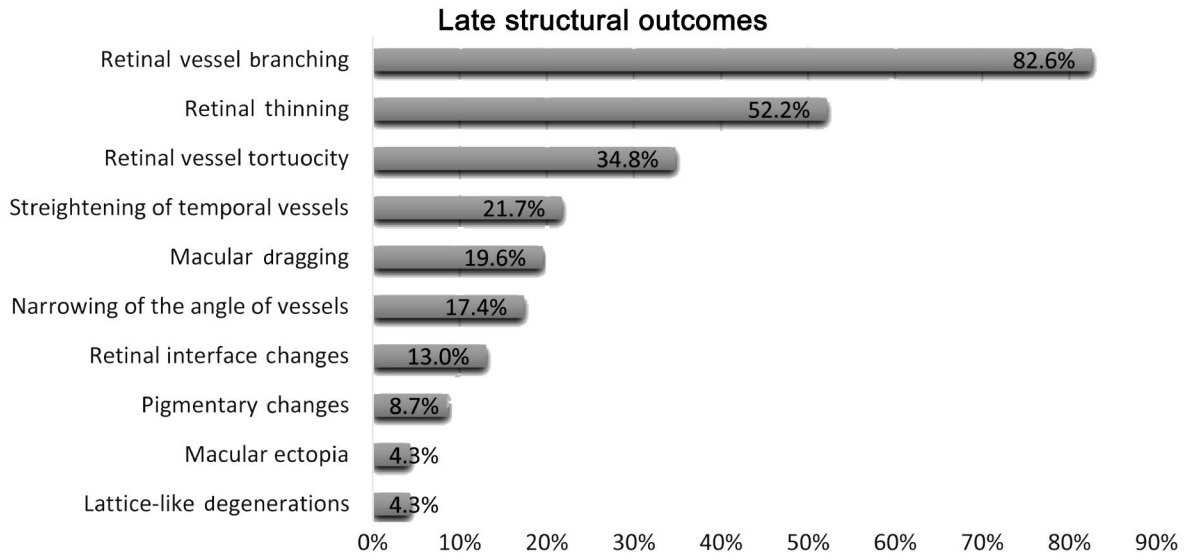

Figure 2 Late retinal structural outcomes of infants treated with temporal 6h cryotherapy.

Streightening of retinal vessels was seen in 21.7% (n=10). Macular dragging was seen in 19.6% (n=9). Narrowing of the angle of retinal vessels at the juxtapapillary entrance were seen in 17.4% of eyes (n=8). Retinal interface changes were seen in 13.0% (n=6), pigmentary changes were seen in 8.7% (n =4) and macular ectopy was detected in 4.3% of the eyes (n =2). Retinal pigment epithelial changes were observable in 11.8% of eyes. One patient had bilateral lattice degeneration (4.3%, n =2) and one patient had bilateral macular ectopia (4.3%, n =2) (Figure 2).

DISCUSSION

The 15y outcomes of the CRYO-ROP trial-which is the largest randomized trial of cryotherapy for ROP-shows that 44.7% of eyes had a distance acuity of ≤20/200 and that 30% showed unfavourable anatomical outcome[15]. Although not exactly comparable, a relatively higher percentage of poor visual outcomes was reported by others; Connolly *et al*[16] (61.9% of 25 patients had CDVA of ≤20/60) and by Jandeck *et al*[17] (82.4% of 46 patients had CDVA ≤20/25). Ng *et al*[18] reported a mean CDVA of 20/182; Shalev *et al*[9] 20/133 and White and Repka[19] reported 20/91 in eyes treated with cryotherapy. In contrast, we had in 67.4% (n =31) of patients with ≤20/200 visual acuity, and the mean visual acuity in our cohort was 20/35 as measured with a Snellen chart. These results are comparable with that of reported long-term outcomes of argon laser photocoagulation. Ospina *et al*[20] reported an overall mean visual acuity of 20/98 in 46 eyes, Shalev *et al*[9]. observed 20/33 in 19 patients, White and Repka[19] measured 20/52 in 19 patients treated with laser. In the final results of early treatment of retinopathy of prematurity (ETROP) study the percentage of patients having unfavorable visual outcome after conventional treatment was reported as 15.2%, where "unfavourable visual acuity" was defined as lower than 1.85 cycle per degree[21]. Although it is not exactly possible to convert spatial frequency values to a Snellen chart, it is important to note that a Snellen equal for 1.85 cycle per degree would be 20/334 when we apply a curve-fit for previously documented cycle per degree to Snellen conversion data[22]. In the CRYO-ROP study, the unfavourable visual outcome was accepted as 20/200, which increases the incidence of "poor visual outcome" in cryotherapy. Here it is also important to note that at the time when cryotherapy was used, early treatment of ROP was not common and it is known that outcomes of conventional treatment are worse[21-23]. Neverthless some reports of of laser treatment are even better up to 6.9% despite a definition of unfavorable visual outcome at 20/200[24].

Our results for the mean spherical equivalent refractive error were also relatively better than the previous reports. The mean spherical refractive error in the present study was -1.76 (-8.00 to 3.00) D and 67.4% of the eyes(n =31) had myopia, and only 8.7% of the eyes (n =4) had a myopia ≥6 D. Shalev *et al*[9] found the mean refractive error was -6.50 D in laser treated ROP patients and -8.25 D in cryo-treated patients. White and Repka[19] reported a similar results with -6.60 D after laser and -7.62 D after cryo-therapy. Vanselow *et al*[25] have found myopia in 55% of eyes that were treated with cryotherapy and high myopia in 29% (≥6 D)[25].

Dhawan *et al*[26] reported in 50.5% of patients (n =193) vascular tortuosity, narrowing of arcades, temporal crescent disc drag or macular heterotopia. Jandeck *et al*[17] reported that temporal dragging of vessels in 15.2% of patients with cryotherapy and in 6.6% of patients treated with laser. In our cohort, the rate of macular dragging was found to be 23.5%. However, mild structural differences might not necessarily effect vision. Wu *et al*[27] have shown that in treated ROP patients the choroid was thinner than those with regressed ROP and thin choroidal thickness was associated with worse

CDVA. In another study ROP patients are reported to have a foveal development abnormality despite a normal seeming posterior pole [28]. It is also important to note that not only retinal structure effects the visual outcome, strabismus and refractive errors are found more frequently in patients with ROP, associated with the severity[29].

In all cases, we applied cryotherapy only to temporal 6h. Our literature search showed only one study comparing long term outcomes of ROP patients treated with 360 degree and partial ablation of the retina which proposed that partial ablation may cause less anatomical changes[30]. We can also speculate that partial ablation of temporal retina may be related with our relatively better late structural outcomes, however it is important to consider several points to in this study; firstly we selected only the patients who were suitable for cryotherapy and thus the patients with a more posterior disease were referred to another clinic and could not be included in the late examination. Another point is that the patients who participated the late examination were only the patients who had good results in our clinic and also had a good general and visual health,who could be brought to our clinic for long term follow up. All of these details may lead to a selection bias.

Although cryotherapy for ROP is largely superseded by laser photocoagulation, as it is highlighted by Simpson *et al*[12]. According to the March 2009 Centre for Evidence Based Medicine rating scale, there is no more than level 2b- rating evidence that supports the shift from cryotherapy to laser treatment. Level 2b- rating corresponds to a sample small size, a follow up loss percentage more than 20% and the lack of masking in the outcome assessment.

Cryotherapy is largely superseded by laser treatment. However our literature search about the late outcomes of ROP treatment revealed more available data for cryotherapy, as laser is a newer treatment method [29]. In this report we primarly aimed to give our late results of "6h cryotherapy" for ROP.

ACKNOWLEDGEMENTS

Conflicts of Interest: Cerman E, None; **Ozarslan Ozcan D,** None; **Celiker H,** None; **Eraslan M,** None; **Sahin O,** None; **Kazokoglu H,** None.

REFERENCES

1 Quinn GE, Fielder AR. Prevention of ROP blindness. *Clin Perinatol* 2013;40(2):xvii-xviii.

2 Sahin A, Sahin M, Türkcü FM, Cingü AK, Yüksel H, Cinar Y, Ari S, Caca I. Incidence of retinopathy of prematurity in extremely premature infants. *ISRN Pediatr* 2014;2014:134347.

3 Multicenter trial of cryotherapy for retinopathy of prematurity. One-year outcome-structure and function. Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Arch Ophthalmol* 1990;108:1408-1416.

4 Laser therapy for retinopathy of prematurity. Laser ROP Study Group. *Arch Ophthalmol* 1994;112(2):154-156.

5 McNamara JA, Tasman W, Vander JF, Brown GC. Diode laser photocoagulation for retinopathy of prematurity. Preliminary results. *Arch Ophthalmol* 1992;110(12):1714-1716.

6 Pogrebniak AE, Bolling JP, Stewart MW. Argon laser-induced cataract in an infant with retinopathy of prematurity. *Am J Ophthalmol* 1994;117(12):261-262.

7 Lambert SR, Capone A Jr, Cingle KA, Drack AV. Cataract and phthisis bulbi after laser photoablation for threshold retinopathy of prematurity. *Am J Ophthalmol* 2000;129(5):585-591.

8 Campolattaro BN, Lueder GT. Cataract in infants treated with argon laser photocoagulation for threshold retinopathy of prematurity. *Am J Ophthalmol* 1995;120(2):264-266.

9 Shalev B, Farr AK, Repka MX. Randomized comparison of diode laser photocoagulation versus cryotherapy for threshold retinopathy of prematurity: seven-year outcome. *Am J Ophthalmol* 2001;132(1):76-80.

10 Hunter DG, Repka MX. Diode laser photocoagulation for threshold retinopathy of prematurity. A randomized study. *Ophthalmology* 1993;100(2):238-244.

11 Cuthbertson F, Newsom R. UK retinopathy of prematurity treatment survey. *Eye (Lond)* 2007;21(2):156-157.

12 Simpson JL, Melia M, Yang MB, Buffenn AN, Chiang MF, Lambert SR. Current role of cryotherapy in retinopathy of prematurity: a report by the American Academy of Ophthalmology. *Ophthalmology* 2012;119(4):873-877.

13 Yenice O, Cerman E, Ashour A, Firat R, Haklar G, Sirikci O, Akman I, Kazokoglu H. Serum erythropoietin, insulin-like growth factor 1, and vascular endothelial growth factor in etiopathogenesis of retinopathy of prematurity. *Ophthalmic Surg Lasers Imaging Retina* 2013;44(6):549-554.

14 Cerman E, Balci SY, Yenice OS, Kazokoglu H, Celiker H, Eraslan M. Screening for retinopathy of prematurity in a tertiary ophthalmology department in Turkey: incidence, outcomes, and risk factors. *Ophthalmic Surg Lasers Imaging Retina* 2014;45(6):550-555.

15 Palmer EA, Hardy RJ, Dobson V, Phelps DL, Quinn GE, Summers CG, Krom CP, Tung B; Cryotherapy for Retinopathy of Prematurity Cooperative Group. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 2005;123(3):311-318.

16 Connolly BP, McNamara JA, Sharma S, Regillo CD, Tasman W. A comparison of laser photocoagulation with trans-scleral cryotherapy in the treatment of threshold retinopathy of prematurity. *Ophthalmology* 1998;105(9):1628-1631.

17 Jandeck C, Kellner U, Heimann H, Foerster MH. Comparison of the anatomical and functional outcome after laser or cryotherapy for retinopathy of prematurity (ROP). *Ophthalmologe* 2005;102(1):33-38.

18 Ng EY, Connolly BP, McNamara JA, Regillo CD, Vander JF, Tasman W. A comparison of laser photocoagulation with cryotherapy for threshold retinopathy of prematurity at 10 years: part 1. Visual function and structural outcome. *Ophthalmology* 2002;109(5):928-934.

19 White JE, Repka MX. Randomized comparison of diode laser photocoagulation versus cryotherapy for threshold retinopathy of prematurity: 3-year outcome. *J Pediatr Ophthalmol Strabismus* 1997;34(2):83-87.

20 Ospina LH, Lyons CJ, Matsuba C, Jan J, McCormick AQ. Argon laser photocoagulation for retinopathy of prematurity: long-term outcome. *Eye (Lond)* 2005;19(11):1213-1218.

21 Early Treatment for Retinopathy of Prematurity Cooperative Group, Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL, Tung B, Redford

M. Final visual acuity results in the early treatment for retinopathy of prematurity study. *Arch Ophthalmol* 2010;128(6):663-671.

22 Drover JR, Wyatt LM, Stager DR, Birch EE. The teller acuity cards are effective in detecting amblyopia. *Optom Vis Sci* 2009;86(6):755-759.

23 Warrasak S, Nawarutkulchai S, Sinsawat P. Functional result and visual outcome in early versus conventional treatment of retinopathy of prematurity. *J Med Assoc Thai* 2012;95 Suppl 4:S107-115.

24 Yang CS, Wang AG, Sung CS, Hsu WM, Lee FL, Lee SM. Long-term visual outcomes of laser-treated threshold retinopathy of prematurity: a study of refractive status at 7 years. *Eye (Lond)* 2010;24(1):14-20.

25 Vanselow K, Kaiser P, Stärk N, Schlösser R, and Zubcov A. Threshold value retinopathy of prematurity. Visual outcome of 2-year-old children after cryocoagulation. *Ophthalmologe* 1999;96(12):786-791.

26 Dhawan A, Dogra M, Vinekar A, Gupta A, Dutta S. Structural sequelae and refractive outcome after successful laser treatment for threshold retinopathy of prematurity. *J Pediatr Ophthalmol Strabismus* 2008;45(6):356-361.

27 Wu WC, Shih CP, Wang NK, Lien R, Chen YP, Chao AN, Chen KJ, Chen TL, Hwang YS, Lai CC, Huang CY, Tsai S. Choroidal thickness in patients with a history of retinopathy of prematurity. *JAMA Ophthalmol* 2013;131(11):1451-1458.

28 Wu WC, Lin RI, Shih CP, Wang NK, Chen YP, Chao AN, Chen KJ, Chen TL, Hwang YS, Lai CC, Huang CY, Tsai S. Visual acuity, optical components, and macular abnormalities in patients with a history of retinopathy of prematurity. *Ophthalmology* 2012;119(9):1907-1916.

29 Gursoy H, Basmak H, Bilgin B, Erol N, Colak E. The effects of mild-to-severe retinopathy of prematurity on the development of refractive errors and strabismus. *Strabismus* 2014;22(2):68-73.

30 Iwase S, Kaneko H, Fujioka C, Sugimoto K, Kondo M, Takai Y, Kachi S, Terasaki H. A long-term follow-up of patients with retinopathy of prematurity treated with photocoagulation and cryotherapy. *Nagoya J Med Sci* 2014;76(1-2):121-128.