Risk factor analysis for long-term unfavorable ocular outcomes in children treated for retinopathy of prematurity

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SUMMARY: Mutlu FM, Küçükevcilioğlu M, Ceylan OM, Altınsoy Hİ, Sarıcı SÜ. Risk factor analysis for long-term unfavorable ocular outcomes in children treated for retinopathy of prematurity. Turk J Pediatr 2013; 55: 35-41.

The aim in this study was to report long-term ocular outcomes of neonates treated for retinopathy of prematurity (ROP) and potential risk factors for unfavorable ocular outcomes. The study consisted of neonates treated for ROP between March 1999 and November 2009. Data relating baseline characteristics and late structural, functional and refractive ocular outcomes were recorded. The association between the unfavorable ocular outcomes and ROP-related risk factors was evaluated by regression analysis. Forty-eight children were included for assessment. Average chronological age at the time of follow-up was 3.11±0.73 years. The rates of unfavorable structural and functional outcomes were 12% and 15.3%, respectively. Ocular deviation was common (27.1%), and mostly esotropic (12/13). A clear myopic tendency was observed (51.2%), and the mean spherical equivalent per eye was –0.72±2.9 diopters. Regression analyses for unfavorable ocular outcomes revealed intraventricular hemorrhage as a core independent risk factor.

In conclusion, ROP treatment has shown promising results in both structure and function. Because of the high risk of developing an unfavorable outcome, a more intense follow-up is required in neonates with a history of intraventricular hemorrhage in the neonatal period. Further studies from other centers are needed to develop a national database, which may validate this observation.

Key words: function, outcome, retinopathy of prematurity, risk factors, structure.

Retinopathy of prematurity (ROP) is one of the few causes of preventable childhood blindness. Ophthalmic screening is required to identify disease that requires treatment whereby the development of potentially blinding disease can be minimized[1]. The Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study, the first multicenter trial, demonstrated favorable results in neonates treated by cryotherapy for threshold ROP defined as at least 5 contiguous or 8 cumulative clock hours of stage 3 disease in zone I or in zone II in the presence of plus disease; the following one year results for unfavorable functional and structural outcome were 35% and 25.7%, respectively[2]. Following that, the Early Treatment for Retinopathy of Prematurity (ETROP) Cooperative Group study, designed to gain better results with treatment at an earlier stage (prethreshold ROP), defined as zone I, any stage ROP with plus disease; Zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease, revealed confirmatory benefits of earlier treatment with laser photocoagulation, and the ratios of unfavorable functional and structural outcomes at the 9th-month follow-up were 14.3% and 9%, respectively[3]. However, in the long-term, this gain in vision and structure was not sustainable, such that results for unfavorable functional and structural outcome were 44.7% and 30% at the 15th-year follow-up of the CRYO-ROP study and 25.1% and 8.9% at the 6th-year follow-up of the ETROP study[4,5]. In that respect, the current concept

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that "ROP is a lifetime disease and follow-up is essential later in life"[6] emerged.

Though there are several studies analyzing the incidence and risk factors of ROP in Turkey, local literature lacks the long-term follow-up data of neonates treated for ROP[7,8]. The aim of this study was to review ocular outcomes of neonates treated for ROP by examining in early childhood (through 2.5 to 5 years of age) and to evaluate the contribution of various neonatal factors to the risk of development of unfavorable ocular outcomes. This may inspire other centers to do further studies, which may in turn help greatly in developing a national database.

Material and Methods

This study consisted of 51 treated out of 609 (8.3%) premature neonates screened between March 1999 and November 2009 in our institution. Approval for the present study was obtained from the Institutional Ethics Committee of our center. Treatment criterion was threshold disease before October 2005 and prethreshold disease thereafter. Written informed consent was taken from the parents before all treatments. All the neonates were screened between 4 and 6 weeks after birth or at a postconceptional age of 31-33 weeks as described previously[9]. The neonates with severe ROP (threshold or prethreshold) were treated either with laser or cryotherapy under general anesthesia within 72 hours.

Follow-up examinations were performed at 3, 6, 9, and 12 months and on a yearly basis thereafter. The last examination of each infant was included in the present study for assessing long-term outcome. One of two experienced pediatric ophthalmologists performed the ophthalmic examination in an alternate fashion such that each examined the child he did not treat. Visual acuity was tested with linear tumbling "E" cards and Snellen charts in verbal children. Visual function was estimated by the presence or absence of normal fixation and presence or absence of nystagmus in preverbal children. Unsteady, uncentral and unmaintained fixation was accepted as unfavorable functional outcome. In verbal children (3 - 5 years), visual acuity results were documented in Snellen equivalent, and visual acuity ≤20/200 was accepted as unfavorable functional outcome. Strabismus was diagnosed by the cover-uncover test and corneal light reflections. Versions were also inspected. Refractive errors were determined by cycloplegic retinoscopy after instilling 1% cyclopentolate hydrochloride. When there was a medical contraindication to this drop, either 0.5% cyclopentolate or 1% tropicamide was used. Slit lamp and dilated fundus examinations were also performed to document structural changes. Presence of partial or total retinal detachment, prephthisis or phthisis bulbi, optic disk dragging, cataract blocking the view of the macula, and total optic disk pallor were considered as unfavorable structural outcomes.

Data including treatment criteria (threshold or prethreshold), birth weight, gestational age, gender, oxygen therapy, mechanical ventilation, respiratory distress syndrome (RDS), sepsis (culture-proven), multiple birth, blood transfusion, intraventricular hemorrhage (IVH), in vitro fertilization (IVF), and outborn status were recorded to assess the risk factors for the main outcome measures (unfavorable functional and structural outcomes). Data were analyzed using SPSS version 15 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL). Logistic regression models were used to determine the relationship of these variables with the development of unfavorable outcome. As the cohort had a limited number of children, variables for which the unadjusted p value was less than .20 and variables thought as clinically significant in univariate logistic regression analysis were identified as potential risk markers and included in the full model. The model was reduced by using backward elimination, and we eliminated potential risk markers by using likelihood ratio tests. A p value less than .20 was considered significant.

Results

Of the original cohort of 51 children, 3 died before 1 year of age and deaths were not related to ROP treatment. We had all the remaining 48 children (18 threshold, 30 prethreshold) checked at least once through 2-5 years of age. There were 25 female and 23 male patients, whose average chronological age at the time of follow-up was 3.11±0.73 years (range: 2.5-5 years). The mean gestational age at birth was 28.06 weeks (range: 25-32), and mean birth

Table I. Baseline Characteristics of Treated Children Evaluated for Long-Term Follow-Up (n=48)

Characteristics	
Birth weight (mean±SD, g)	1100±311
Gestational age (mean±SD, wk)	28.06±2.04
Gender (Male, %)	47.9
Multiple births (%)	
Single	50
Twin	47.9
Triplet	2.1
Inborn/Outborn (%)	
Inborn	81.2
Outborn	18.8

Table II. Type of Treatment Modalities Performed in Treated Eyes (n=91)

Treatment modality	n (eyes)
Primary ablative	
Diode laser photocoagulation	71
Cryotherapy	16
Combined laser+Cryotherapy	4
Supplementary	
Intravitreal bevacizumab injection	
Primary	1
Adjunctive	5
Retinal surgery	
Encircling	2
Vitrectomy with silicone oil	4
Encircling+vitrectomy with silicone oil	4

weight was 1100.52 g (range: 660-2140). Of those children who returned, 43 (89.6%) had bilateral treatment and 5 (10.4%) had unilateral treatment for severe ROP, yielding a total of 91 treated eyes. The mean timing of treatment was 37.2 weeks (33-44). Table I displays the baseline characteristics of the 48 treated children. There were four neonates with zone I disease, and one of them with stage 4 was referred from a different center for further clinical evaluation. Primary ablative treatment was performed as follows: Transpupillary diode laser photocoagulation (78.1%); cryotherapy at the very beginning of the study period or when visualization of the retina was obscured by a rigid pupilla or a blurry optical media (17.5%); and laser and cryotherapy alternately depending on the pupillary rigidity or media clarity (4.4%). Intravitreal 0.75 mg bevacizumab (Avastin, Genentech, USA), a vascular endothelial growth factor (VEGF) antibody injection, was performed primarily in one eye of a neonate for stage 4a ROP as a salvage therapy, and adjunctively to ablative therapy in zone I aggressive posterior ROP (6.6%)[10]. Table II displays the treatment modalities performed during the study period. No life-threatening side effect was observed during the first-line therapy with cryotherapy or transpupillary diode laser photocoagulation. Though we routinely prescribed each neonate topical steroid and antibiotic drops for a week after ablative therapy, both eyes of a neonate developed resistant anterior chamber inflammation relieved at the end of a three- week follow-up with a resultant posterior synechia at the 6 o'clock position on the left eye. No severe posterior segment side effects were observed except for slight hemorrhages in 15% of the eyes, which were absorbed spontaneously during follow-up. Vitreoretinal surgery was needed in 10 eyes of 7 patients for stage 4 and 5 ROP (2 encircling, 4 vitrectomy with silicone oil, 4 encircling followed by vitrectomy with silicone oil). In one of the neonates, encircling surgery bands were removed later from both eyes. Despite this struggle, 8 eyes of 5 patients ended up blind (less than 20/500, according to World Health Organization).

Structural Outcome

We encountered structural change of any severity in 21 eyes of 13 patients: 5 progressed to stage 5, 3 ended up prephthisic or phthisic, 1 had papillary dragging, 10 showed optic disk pallor to some degree (1 with total, 3 with temporal hemi-disc and 6 with sectoral), and 2 had cataract. Totally, 11 out of 91 eyes (12%) showed unfavorable structural outcome at the follow-up. One of the prephthisic eyes developed phacomorphic glaucoma after lens-sparing vitrectomy and underwent lens aspiration without intraocular lens implantation. Of the remaining 2 children with cataract, one, treated with laser, had a partial cortical cataract not disturbing the visual axis, but the other, treated surgically, had a posterior subcapsular cataract obscuring the view of the macula (Table III).

Visual and Refractive Outcome

There were 20 preverbal (<3 years) and 28 verbal (3-5 years) children. Of the 91 treated eyes, 14 (15.3%) had significantly reduced vision (≤20/200 in verbal children and uncentral/unsteady/unmaintained fixation in preverbal children), and 8 of them (8.7%) were

Table III. Structural and Functional Ocular Outcomes of Treated Children

Outcome	n (eyes)	% (eyes)
Unfavorable functional outcome*	14	15.3
Blindness	8	8.7
Unfavorable structural outcome	11	12
Stage 5	5	5.5
Prephthisis - Phthisis	3	3.3
Papillary dragging	1	1.1
Total optic disk pallor	1	1.1
Cataract (obscuring macula)	1	1.1
Favorable structural outcome	10	10.9
Partial optic disk pallor	9	9.9
Cataract (partial cortical)	1	1.1

*: Visual acuity ≤20/200

legally blind. Thirty-five patients (72.9%) were orthotropic, while 12 (25%) were esotropic and only 1 (2.1%) exotropic. Mean angle of deviation was 22 prism diopters. Two esotropic patients underwent strabismus surgery. Three patients (6.2%) had some form of nystagmus. Overall functional and structural outcomes are given in Table III.

The mean spherical equivalent per eye was –0.72±2.9 diopters (D), when 8 eyes of 5 children with stage 5, prephthisis and phthisis were excluded. The majority of values ranged between +5 D and -6 D. Of the remaining 83 eyes, 44 (53%) were myopic, 34 (40.9%) were hypermetropic and only 5 (6.1%) were emmetropic. Astigmatism ranged from 0 to 3.5 D (mean 2.8 D), and astigmatism of ≥1 D and astigmatism of ≥2 D were present in 40.6% of eyes and 11.6% of eyes, respectively. In all, 46 eyes (55.4%) had with-the-rule astigmatism and 6 (7.2%) had against-the-rule astigmatism. Three children (3.6%) had a difference greater than 1 D between the degree of astigmatism of their eyes.

Regression Analysis

The logistic regression model for unfavorable structural outcome revealed gestational age, multiple birth and IVH as significant risk factors. However, only IVH (p=0.162) was found to be an independent determinant in multivariate analysis (Table IV). While the second regression model for unfavorable functional outcome revealed gestational age, RDS, sepsis, and IVH as significant risk factors, again IVH (p=0.127) was the only one to be

Table IV._Univariate and Multivariate Analyses of the Risk Factors for Unfavorable Structural Outcome

Risk factors	Crude OR	CI 95%	p	Adjusted OR	CI 95%	p
Treatment criteria (Threshold vs prethreshold)	0.389	0.076-1.985	.256			
Birth weight (g)	1.000	0.997-1.002	.891			
Gestational age (wk)	0.740	0.464-1.181	.207	0.821	0.104-6.512	.852
Oxygen therapy	0.686	0.160-2.946	.612			
Gender	0.636	0.110-3.694	.614			
Respiratory distress syndrome	1.771	0.307-10.227	.523			
Mechanical ventilation	1.270	0.252-6.400	.772			
Multiple birth	2.155	0.484-9.600	.214	2.397	0.499-11.514	.275
Blood transfusion	1.043	0.207-5.268	.959			
Sepsis	1.544	0.306-7.785	.599			
Intraventricular hemorrhage	3.222	0.624-16.631	.162	3.222	0.624-16.631	.162
In vitro fertilization	1.045	0.166-6.604	.962			
Outborn	1.943	0.312-12.118	.477			

OR: Odds ratio. CI: Confidence interval.

Table V. Univariate and Multivariate Analyses of the Risk Factors for Unfavorable Functional Outcome

Risk factors	Crude OR	CI 95%	p	Adjusted OR	CI 95%	p
Treatment criteria (Threshold vs prethreshold)	0.700	0.161-3.040	.634			
Birth weight (g)	0.999	0.996-1.002	.416			
Gestational age (wk)	0.719	0.469-1.103	.131	2.008	0.493-8.175	.331
Oxygen therapy	1.270	0.252-6.400	.772			
Gender	0.686	0.160-2.946	.612			
Respiratory distress syndrome	2.705	0.497-14.718	.250	1.366	0.193-9.662	.754
Mechanical ventilation	0.895	0.242-3.307	.868			
Multiple birth	1.839	0.480-7.037	.374			
Blood transfusion	1.714	0.374-7.855	.488			
Sepsis	2.588	0.564-11.876	.221	1.818	0.304-10.895	.513
Intraventricular hemorrhage	3.182	0.718-14.094	.127	3.182	0.718-14.094	.127
In vitro fertilization	0.636	0.110-3.694	.614			
Outborn	1.306	0.222-7.680	.768			

OR: Odds ratio. CI: Confidence interval.

an independent determinant (Table V).

Discussion

In Turkey, treatment rates for ROP seem to be higher than those of the developed world (range: 3.1% - 11.5%)[11-13]. The rate of 8.3% in the present study fell within this wide range; however, lack of population-based data and a national screening algorithm preclude making reliable assumptions. Management of ROP in accordance with western guidelines in Turkey has offered promising results, but long-term follow-up data of neonates with regressed or treated ROP have not been reported yet. Even in the developed world, where there is strict adherence to computer-based follow-up programs, a significant proportion of treated neonates are lost to follow-up and another significant proportion develop severe visual disability caused by ROP[14]. That is why we need to establish a national database consisting of long-term follow-up data of a large population of ROP cases to obtain figures comparable with those of the developed world.

In our study, the rate of unfavorable functional outcome was 15.3%. It was lower than that of CRYO-ROP's age-matched reports and was comparable with ETROP's initial report[3,15-17]. As our cohort included neonates from different age groups and with different treatment modalities, a head-to-head comparison of these studies is not suitable. Some other small-scale single-center studies reported rates of unfavorable functional outcome within a range between 5-36% for neonates treated with laser or cryotherapy[18-22]. Out of 10 eyes that needed vitreoretinal surgery, only 8 (8.7% of all treated eyes) ended up blind in the present study. However, this rate was 15.1% in O'Keefe et al.'s study[21], 32.6% in the 5.5-year report of the CRYO-ROP study and 9% in the 6-year report of the ETROP study[5,16,21]. Although the present study reports the outcomes of ROP treatment performed in accordance with two different criteria (threshold and prethreshold), the given rates of functional outcome were comparable with those of the treatment arm of the ETROP study, probably due to dominancy of neonates treated for prethreshold ROP. However, heterogeneity arising from the differences between parameters such as mean age at the follow-up examination and testing method for visual acuity assessment precludes a reliable evaluation.

Structural benefit exceeded functional outcome with a rate of 12% in the present study. Similarly, this observation was almost always constant in all long-term reports of both the CRYO-ROP and ETROP studies[3-5,15-17]. Possible explanations were the detrimental effect of ROP on visual acuity and prematurity-related central nervous system changes that are common in these neonates. As seen in functional outcome data, structural outcome was comparable with that of ETROP. In brief, almost 90% of the eyes had a favorable result in terms of both

structure and function.

There was a large range of refractive outcomes observed in the present study, and nearly half of the children were myopic, which supports the myopic tendency stated in previous reports[17,20,22]. Similar to the results of the ETROP study, astigmatism was also prevalent in the present study[23]. Though there are many differences between the present and previous studies, we could make a limited assumption that all treatments we performed did not put the neonates at a risk for astigmatism exceeding the rate given by ETROP.

Strabismus is a common associated finding in premature neonates with ROP. The ETROP study group reported rates of 20.1% and 30.3% for the neonates with high-risk ROP at 6 and 9 months, respectively, and three-fourths of them were esotropic[24]. We found a rate of 27.1% for our cohort, with a mean age of 2.53±0.64 years, and only one was exotropic. Conforming to the idea that strabismus in these children has a variable nature, we approached more conservatively so that only two children underwent strabismus surgery[24]. The remaining 10 (2 with sensorial deviation due to severely impaired vision, 3 with a neurologic abnormality and 5 with an angle of deviation less than 15 prism diopters) were assigned to clinical observation.

One of the most important risk factors associated with any kind of unfavorable ocular outcome is reportedly gestational age of the neonate[25]. We found gestational age as an important risk factor in univariate analysis, though it was insignificant in multivariate analysis regarding both unfavorable structural and functional ocular outcomes in the present study. Although IVH is closely related with the development of severe ROP in the neonatal period[26], there has been no study investigating the association between early (neonatal) IVH and late (early childhood) unfavorable ocular outcomes, and the present study demonstrates this association in multivariate analysis.

We are aware that this long-term study has some limitations: the small sample size, its single- center nature, the different treatment modalities with two different treatment criteria, the wide range for follow-up age, and the qualitative assessment of functional outcome below three years of age. The limited number of children in the present study may have caused low statistical power of risk factors in regression models, but the study presents some strong clues about the relationship between the presence of IVH and unfavorable ocular outcomes. Ng et al[27]. and Hungerford et al[28]. previously studied the relationship between cerebral damage (ischemic or hemorrhagic) and severity of ROP. Results of the present study corroborate this hypothesis with a clear increase in the risk of developing severe ROP and developing unfavorable ocular outcomes later. However, further studies with large sample sizes are needed to establish a more consistent statistical model to determine this crucial correlation.

In conclusion, ROP treatment during the last decade has shown promising results relating to both structure and function in the long term. Furthermore, presence of IVH seems to put the neonates into a high-risk category for developing an unfavorable ocular outcome, and the follow-up schedule should be more intense in these neonates. However, we need broad population-based data to ascertain this observation.

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