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Original Article

Long term visual outcomes in laser treated threshold retinopathy of prematurity in Central Saudi Arabia

Abdullah G. Al-Otaibi, MD*; Sultan S. Aldrees, MD; Ahmed A. Mousa, PhD

Abstract

Purpose: To assess the long term visual outcomes and refractive status of patients who underwent diode laser for threshold retinopathy of prematurity (ROP) and to investigate the risk factors leading to poor visual outcomes.
Methods: Fifty-seven patients (114 eyes) with threshold ROP who underwent laser therapy were contacted for reassessment. A chart review was performed for all patients to collect data on visual acuity, retinal status and strabismus. A favorable visual outcome was defined as ⩾20/160 (Snellen acuity) for young adults (cooperative patients), and ⩾CSM for children (uncooperative patients) while unfavorable visual outcome was defined as <20/160 or <CSM. Vision in uncooperative children was graded as central, steady, maintain. Descriptive and inferential analyses were conducted. Chi^2 and odds ratios were calculated whenever appropriate. A P value <0.05 was considered as statistically significant.
Results: The mean age at reassessment was 5.2 ± 2.5 years (range, 1–10 years) where 36 (63.2%) patients were males and 21 (36.8%) were females. Out Of the 114 laser treated eyes, 73 (64%) were myopic, with mean spherical equivalent (SE) of −6.69 (5.9), range (−0.25 to −21) diaopters, 8 (7%) were emmetrope, while other 33 (29%) were hyperopic with mean SE of +2.43 (3.04), range (+0.25 to +17) diaopters. Strabismus was present in 31 patients (54.4%) of whom 81% (25/31) were esotropic. Retina was found to be normal in 77.1% of the examined eyes, while the remaining eyes had either macular dragging or retinal detachment. Almost 70% of the eyes with a normal retinal examination had favorable visual outcome. Thirteen (11.4%) eyes had zone 1 retinopathy, 83 (72.8%) eyes had zone 2 retinopathy and 2 (1.8%) eyes had zone 3 retinopathy. Vitreous hemorrhage was present in 7 (6.1%) eyes prior to laser treatment. The relationship between final retinal status and visual outcome was statistically significant ($P < 0.0001$). There was no statistically significant correlation between visual outcome and the zone of the retinopathy ($P = 0.448$).
Conclusion: The majority of patients who underwent diode laser therapy for threshold ROP had favorable anatomical and visual outcomes. However, high refractive error and strabismus may be clinically the pertinent causes of visual impairment.

Keywords: Visual outcomes, Laser therapy, Retinopathy of prematurity, Saudi Arabia

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Introduction

Retinopathy of prematurity can lead to blindness in premature infants without timely treatment. Cryotherapy was the original ablation produce for the retina but it has been superseded by laser photocoagulation. The advantage of laser photocoagulation is the reduction of unfavorable structural outcomes and improved functional vision. Future treatment modalities may include the use of anti-vascular endothelial growth factor (Anti-VEGF) therapies.[1] The outcomes of a 7 year study of underweight newborns (<2000 g at delivery) indicate that 22.2% of premature infants had ROP.[2]

The (CRYO-ROP) study reported a 50% reduction in the incidence of retinal detachment after cryotherapy for thresh-

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Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

* Corresponding author. Address: Pediatric Ophthalmology, Department of Ophthalmology, King Abdulaziz University Hospital, Saudi Arabia. Tel.: +966 1 4775723; fax: +966 1 4775724.
e-mail address: abughazi2001@yahoo.com (A.G. Al-Otaibi).

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old disease[3] with better functional and structural outcomes compared with control eyes.[4] Early treatment of pre-threshold ROP significantly reduces unfavorable functional and structural outcomes.[3]

The current study evaluated the long term visual outcomes and refractive status in patients who underwent diode laser therapy for threshold ROP and investigated the causes of poor visual outcomes.

Methods

The study cohort was comprised of 114 eyes of 57 consecutive patients who underwent diode laser treatment for ROP at King Abdul Aziz University Hospital (KAUH), Riyadh, Saudi Arabia. These patients were contacted for assessment. The mean age of recruited patients was 5.2 ± 2.5 years (range, 1–10 years). The study was performed between July 2010 and Nov 2010, where premature infants who weighed less than 2000 g of birth body weight or were less than 32 weeks of gestational age were screened for ROP in the neonatal intensive care unit by an ophthalmologist.

Patient charts of 145 patients, who were admitted to KKUH from 1995–2010 and underwent diode laser therapy for symmetrical threshold disease, were recruited. Data were retrospectively collected from the medical records. Of the 145 patients, 88 were not included in the study due to parental refusal, insufficient contact data, travel, and death unrelated to eye diseases. The remaining 57 premature infants were contacted and examined. The study was conducted after approval from the ethics committee of the institution and adheres to the tenets of the Declaration of Helsinki.

At first ophthalmic examination, high risk premature infants were screened at a Post-natal age of 4–6 weeks with indirect ophthalmoscope. The stage and severity of ROP were classified according to the International Classification of ROP.[5] Follow up of retinal examination was performed every 1–2 weeks until ROP regression, complete vasculogenesis of retina, or development of threshold ROP. Infants with threshold eyes disease received diode laser photocoagulation within 48 h of diagnosis. The setting of laser treatment was 250–300 mW with a creamy-white laser intensity, using a near confluence pattern placed to the retinal avascular zone anterior to the fibro-vascular ridge.

Structural assessment

Indirect ophthalmoscopy was performed to detect any structural sequelae, including macular distortion or dragging, macular folds, or tractional retinal detachment.

Orthoptic assessment

A trained Orthoptist performed the orthoptic assessment that included evaluation of ductions and versions cover/uncover testing, and alternate cover testing to detect the presence of manifest and latent strabismus. If a child presented with manifest strabismus, then a prism cover test was used to measure the angle of deviation at distance and near fixations. The presence or absence of strabismus was evaluated as an indicator for the potentiality to get amblyopia as a cause of visual deficit.

Visual acuity

The best corrected visual acuity (BCVA) was determined with Snellen optotype chart at 6 m. Central, steady, maintain fixation (CSM) was used for children who are not able to perform optotype acuity (young or mentally disabled). Visual acuity of 20/160 or better was considered a favorable visual outcome, and worse than 20/160 was considered an unfavorable visual outcome.

Refraction

Cycloplegic refraction was determined with retinoscopy or an autorefractometer after installation of 1% cyclopentolate hydrochloride. Refractive errors were converted into spherical equivalent. Myopia was divided into three categories based on magnitude: severe (more than 6 D), mild (0.25–3 D) and moderate (>3–6 D).The refractive error of each eye was evaluated. All study subjects were under the ongoing care of a pediatric ophthalmologist.

Statistical analysis

Data were collected and stored in an excel sheet (Microsoft Office® 2007; Microsoft Corp., Redmond, WA, USA). After data management, data were analyzed using SPSS version 19 (IBM Corp., Armonk, NY, USA), and StatsDirect version 6.1 (StatsDirect Ltd., Cheshire, UK). Descriptive analysis included describing the sample in terms of demographic characteristics. Inferential analysis included the Chi^2 test to investigate the relationship between categorical variables, while Odds Ratio was calculated to investigate the association between ROP and potential risk factors. Confidence intervals of 95% and a corresponding $P < 0.05$ were considered statistically significant. An odds ratio that does not include one was considered statistically significant.

Results

The study cohort was comprised of 114 eyes of 57 patients who underwent diode laser photocoagulation for symmetrical threshold disease. Out of 57 patients, 36 (63.2%) were males and 21 (36.8%) were females. In the majority of patients; 44 (77.2%) were of Saudi nationality. The mean (±SD) birth weight at baseline was 896.9 ± 331.5 g, (range, 400–1800 g), and, the average gestational age was 26.5 ± 3.1 weeks (range, 21–41 weeks). The average duration between onset of disease to presentation at a hospital and diagnosis was 8.7 ± 3.8 months (range, 1–17 months). The mean follow up period was 5.2 years (range, 1–10 years).

Orthoptic results

In the majority of cases; 14 (42.4%) patients used their right eye for fixation more than their left eye; 7 (21.2%) patients and there were 4 (12.1%) patients with alternating fixation. Exotropia was present in 31(54.4%) patients with a mean of 27 ± 8.4 prism diopter (pd) (range, 16–40 pd). Esotropia was present in 25 (43.9%) patients with a mean of 24.8 ± 14.6 pd (range, 3–50 pd). Nystagmus was present in only 5 (8.8%) patients.

Anterior segment status

The majority; 108 (94.6%) of eyes had a normal anterior segment while 2 (1.8%) eyes had cataract and other 2 (1.8%) eyes had post-synechiae.

Classification of the disease

Based on the international method of classification, a considerably large number of eyes were affected in Zone II (83 (72.8%) eyes), followed by Zone I (13 (11.4%) eyes) and Zone III (2 (1.8%) eyes). Additionally, 9 (7.9%) eyes were at the pre-threshold stage, and 7 (6.1%) eyes had a vitreous hemorrhage.

Structural assessment of the retina

Funduscopy showed that 88 (77.1%) of the cases had a normal retina, while 12 (10.5%) cases had macular dragging, 5 (4.4%) cases had retinal detachment, 7 (6.2%) cases had pale optic disk, and 2 (1.8%) cases had end stage ROP.

Visual outcomes

Twenty-eight patients (56 eyes) were cooperative for visual acuity testing who had a mean age of 6.8 ± 1.9 years, (range, 3–10 years) constituted 49.1% of the study population, 21.1% (24 eyes) of them had a visual acuity of ⩾20/40 and 15 eyes (13.2%) had visual acuity in the range of 20/50–20/160, 13 (11.4%) eyes had visual acuity 20/200 to light perception and 4 (3.5%) eyes had no light perception. Among the 29 uncooperative children (58 eyes) who could not perform the Snellen acuity test, 45 (39.5%) eyes had CSM, 6 (5.3%) eyes had CSUM, 2 (1.8%) eyes had CUSUM and 5 (4.4%) eyes had UCUSUM.

A favorable visual outcome defined as ⩾20/160 or ⩾CSM was noted in 84 (73.7%) eyes while unfavorable visual outcome defined as <20/160 or <CSM was noted in 30 (26.3%) eyes (Table 1).

Table 1. Visual acuity outcomes of patients who underwent diode laser treatment for retinopathy of prematurity.

Cooperative patients[a]	*N*	Percentage (%)
⩾20/40	24	21.1
20/50–20/160	15	13.2
20/200–LP	13	11.4
NLP	4	3.5
⩾20/40	24	21.1
20/50–20/160	15	13.2
20/200–LP	13	11.4
NLP	4	3.5
Uncooperative patients[b]		
CSM	45	39.5
CSUM	6	5.3
CUSUM	2	1.8
UCUSUM	5	4.4
Total Favorable ⩾20/160 or ⩾CSM	84	73.7
Total Unfavorable <20/160 or <CSM	30	26.3

[a] Cooperative patients were patients who could read Snellen letters during visual acuity testing.

[b] Uncooperative patients were patients who were too young or otherwise unable to perform the Snellen acuity CSM denotes central, steady, maintain.

Refraction

Eight (7%) of the eyes were emmetropic. The majority of eyes were myopic 73 (64%) with mean spherical equivalent (SE) of −6.69 (5.9), range (−0.25 to −21) diaopters, while other 33 (29%) were hyperopic with mean SE of +2.43 (3.04), range (+0.25 to +17) diaopters. The mean spherical equivalent of the study cohort was −3.7 ± 6.5 D. (Table 2).

There was a highly statistically significant association between the presence of a retinal abnormality at baseline and an unfavorable visual outcome postoperatively ($P < 0.0001$). There was no statistically significant association between while the zone of the disease and sex of the patient were with visual outcomes ($P = 0.448$ and 0.603, respectively).

Other statistically significant potential risk factors that may lead to unfavorable visual outcomes were: gestational age ($P = 0.014$) esotropia ($P = 0.049$) ($P = 0.580$) and presence of refractive errors ($P = 0.016$).

Discussion

Favorable functional and structural outcomes of laser treated ROP eyes compared with cryotherapy have been previously reported.[6–9] However, the current study presents the long term structural and visual outcomes of laser treated threshold ROP with large cohort and a mean age of 5.2 years (range, 1–10 years). According to Yang et al., many patients with favorable structural outcomes suffered from impaired visual function on long term follow up.[6] Yang et al. suggested some variables that may contribute to the poor visual outcomes including myopia, strabismus, prenatal neurologic events and anisometropia which were significantly associated with poor visual outcomes in ROP patients treated with laser ($P = 0.002$).[6]

We found that 64% of our study cohort were myopic of which 28.9% had more than 6.0 D of myopia. Yang et al.[6] reported similar that results with 77% of 60 eyes were myopic of which16.7% had more than 6.0 D of myopia. Yang et al.[6] reported a mean spherical equivalent of −3.87 D which was clinically negligible from 3.7 ± 6.5 D in our study. McLoone et al.[7] also reported similar results with 50% of 43 eyes that underwent laser therapy for ROP were myopic with 35% having myopia greater than 4.0 D (Table 3). White and Repka performed a 3 year follow up of and reported comparable structural outcomes and better functional outcomes compared to cryotherapy.[8] In White and Repka's study, the laser treated group was myopic with a mean spherical equivalent of −6.6 D.[8] The difference between the outcomes of White and Repka's study and our study maybe partially related to the differing sample size between both studies (57 patients in our study vs 12 patients), although the mean follow up

Table 2. Refractive errors of patients who underwent diode laser treatment for retinopathy of prematurity.

Type of refraction	Number	Percentage (%)
Mild myopic	25	21.9
Moderate myopic	15	13.2
Severe myopic	33	28.9
Emmetrope	8	7
Mild hyperopic	22	19.3
Moderate hyperopic	9	7.9
Sever hyperopic	2	1.8

Table 3. Refractive outcomes reported in various studies of laser therapy for retinopathy of prematurity.

Authors	No. of eyes	Laser	Follow up (years)	Mean spherical equivalent
McLoone et al.[7]	37	Diode	11	−2.1 D
Ng et al.[13]	20	Argon and diode	9.9	−4.48 D
Opsina et al.[14]	42	Argon	6.2	−4.95 D
Yang et al.[6]	60	Diode	7.8	−3.87 D
Current study	114	Diode	5.2	−3.7 D

period, mean birth weight and gestational weeks were almost similar. Shalev et al.[9] performed an extended follow up of (7 years) and reported a minimal reduction of myopia in the laser treated groups.

The association between myopia and ROP has been recognized with an increase in the incidence among severe and low birth weights. Various hypotheses have been proposed for the cause of myopic fundi including; shallow AC, axial length and high crystalline lens power.[7,10,11] Tasman et al.[12] proposed that retinal detachment associated with myopic fundi is a predominant finding in retinopathy of prematurity.

The cryo-ROP study group reported visual acuity of 20/40 or better in 25.2% of the treated versus 23.71% of non treated eyes.[15] Smaller comparative studies have found good visual outcomes in the group of eyes treated with laser.[8,9] In our study we have divided the patients into two groups based on their visual acuity. Visual acuity $\geqslant$20/160 or $\geqslant$CSM was achieved in 73.7% the study cohort indicating good functional success of laser therapy.

More than half of the cohort (54.4%) had strabismus of which 43.9% had esotropia. Esotropia is significantly associated with poor visual outcomes ($P = 0.049$) but not exotropia. Yang et al.[6] reported a 30% incidence of strabismus with more than half of the cases were esotropic. Yang et al.[6] also found that most common concomitant conditions with strabismus were perinatal neurological events (e.g. periventricular leucomalacia, intraventricular hemorrhage), anisometropia, high myopia and unfavorable anatomical outcomes. The incidence of strabismus increases by 34% in regressed ROP patients compared to neonates without ROP (16%). Furthermore it increases with the severity of ROP.[16–18] Nystagmus was present in a very few number of patients (8.8%) which was statistically insignificant in affecting visual outcomes. This outcome concurs with a study by McLoone et al.[7] who reported 12% of 37 patients with nystagmus.

Almost 75% of our patients had favorable structural outcomes, with only 22.9% having some sort of macular cdragging, retinal detachment, pale optic disk and end stage ROP. The correlation of abnormal retinal structure with poor visual outcomes was statistically significant ($P = 0.0001$). Yang et al.[6] reported 1.7% of the treated eyes with abnormal retinal structure, but 34.5% had unfavorable visual outcomes, indicating other factors leading to poor visual outcome such anisometropia, high myopia, nystagmus. McLoone et al.[7] reported 10 eyes with poor visual outcomes of which only three had poor structural outcomes. Opsina et al.[14] reported that abnormal retinal structure rarely causes poor visual outcomes after laser therapy for ROP compared to factors such as strabismus, amblyopia and perinatal neurological events.

Some potential limitations of our study included the retrospective analysis and the non- randomized study design in addition to some data were missing from the patient charts. The large sample size made detailed analysis of each individual case tenuous at best. Other drawbacks of the study were that we did not assess some variables which are believed to be associated with poor visual outcomes such as anisometropia, astigmatism and perinatal neurological events. However, the large sample size of our study population and long term follow up is an advantage as it provides more accurate results regarding the potential variables and their association with the structural and visual outcomes.

Laser treatment for ROP can result in complications, including corneal haze, iris and tunica vasculosa lentis, and constricted visual field.[19–25] In our study, 2% of the cohort had cataract. However causation from laser therapy or other factors remain inconclusive due to our study design.

In conclusion, the majority of patients with diode laser therapy had favorable visual and structural outcomes. However strabismus and high refractive errors remain the important causes of impaired visual function. Early detection and timely treatment reduce the associated morbidity. A special emphasis should be placed on early detection and treatment of ROP to decrease the unfavorable outcomes of laser treated eyes.

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