Ophthalmologic outcome of premature infants with or without retinopathy of prematurity at 5-6 years of age

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ABSTRACT

Purpose: Vision is the main source of sensory information to the brain in most species of living and human beings and is one of the most important senses for the normal physical and mental development of children. Retinopathy of Prematurity (ROP) is one of the leading causes of blindness and visual impairment worldwide. Refractive errors such as myopia, astigmatism, and anisometropia are common in premature infants with or without ROP. Methods: A prospective cohort study was performed on the population of premature infants. Screening for Retinopathy of Prematurity in neonatal period was performed according to the protocol of ophthalmologic examination and between 4 and 6 weeks after birth by retinal specialist. The case group included 90 children with or without ROP during infancy. Primary and measurable outcomes in the studied children, including visual acuity, refractive errors, strabismus, and amblyopia, were assessed by an optician and retina ophthalmologist. Results: In our study, at the age of 5-6 years, 26.67% of case group and 48.89% of control group had visual impairment. Amblyopia 3.33%, strabismus 6.67%, and refractive errors 16.67% were found in the case group. In control group amblyopia was reported 12.22%, strabismus 6.67%, and refractive errors 30%. In this study, visual impairment was higher in the control group than in the case group. Conclusion: Considering the high prevalence of visual impairment in the control group children who were all without ROP, it is necessary to emphasize the importance of careful visual examination of the children at a younger age and remind them of the importance of visual impairment.

Keywords: Ophthalmologic outcome, premature infants, retinopathy of prematurity

Introduction

The future of every society depends on the health of its children and will remain a sustainable society that succeeds in maintaining the health of its children. Vision is the main source of sensory information to the brain in most species of living and human beings and is one of the most important senses for the normal physical and mental development of children. Visual perception allows one to make accurate judgments of the size, shape, and spatial relationship of objects. The person to carry out everyday activities require visual information processing.[1]

According to WHO statistics, approximately 153 million people suffer unrecorded refractive vision each year, which includes children. There is no doubt that visual impairments have a significant impact on a child’s learning ability and severe unrecognized refractive errors have a significant impact on the

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child’s development, resulting in academic failure and impaired learning ability.[3]

Retinopathy of prematurity (ROP) is one of the leading causes of blindness and visual impairment around the world. Refractive errors such as Myopia, Astigmatism, and Anisometropia are common in premature infants with or without ROP.[4,6]

Preterm birth, low birth weight, and high severity of Retinopathy of Prematurity are known risk factors for developing strabismus. Even among a number of children with favorable structural and visual outcomes in both eyes, the prevalence of strabismus at age 6 has been reported at 26%.[5]

As reported in previous studies, prematurity, stress, and postnatal diseases may alter the natural process of eye development. Therefore, the necessity of evaluating premature infants at preschool and school age is to confirm the long-term refractive effect.[5,6] Also, studies show that approximately 66.67% of eyes with high-risk ROP during infancy are likely to have myopia during preschool and early school years.[7-9]

We concluded that due to increased eye problems and visual impairments and high rate of ROP as a factor of strong influence on visual impairment and since Retinopathy of Prematurity is potentially an avoidable cause of blindness in infants and children and leads to a wide range of outcomes,[10] in a cohort study, we examined the ophthalmologic outcome in premature infants at the age of 5–6 years in Babol city.

Martials and Methods

A prospective cohort study was performed on premature infants in Babol city. Sampling was done by available method. In this study, premature infants were admitted to the neonatal intensive care units of Shafii'zadeh Amirkola Children's Hospital and Babol Ayatollah Rouhani Hospital from April 2011 to December 2012: 1. had a birth weight of 2000 grams or less 2. gestational age 34 weeks or less.

Screening for ROP in neonatal period was performed according to the protocol of ophthalmologic examination and between 4 and 6 weeks after birth by retinal specialist. The stage and severity of ROP were determined according to the International Classification of ROP (IC-ROP) for each premature infant and neonates in need of treatment were treated with Avastin.

Case children included 90 premature infants who had or without ROP. Premature infants with ROP had progression or regression. Infants undergoing regression progressed to normal vascularization, and infants with progressive and needing treatment were treated with Avastin injections.

The control group’s children (90 children) were in term neonates and had no history of neonatal intensive care unit admission. Also, without congenital ocular disease and congenital malformations associated with ocular involvement. The case group at the age of 5–6 years was compared with a matched control group. We used Chi-square and Mann-Whitney statistical methods to compare between groups.

Primary and measurable outcomes in the studied children, including visual acuity, refractive errors, strabismus, and amblyopia, were assessed by an optometrist and retina ophthalmologist. The visual acuity of these children was assessed with a Snellen chart (E chart) within 6 m. Ocular motility, nystagmus and strabismus were also measured by Cover Test at 30 cm and 6 m. Refractive errors were evaluated by a retinoscope, BETA200, Germany-HEINE, and Cyclopentolate eye drops. When the retinoscope was unavailable, the Japan-Topcon 6500 autorefractometer was used with a Cyclopentolate eye drop.

The refractive errors criterion is considered significant in Hyperopia ≥+3.00D, in Myopia ≥−3.00D and in Astigmatism ≥2.00D (negative cylinder). The Anisometropia is also ≥2.00D. In the amblyopia examination BCVA (Best Correction Visual Acuity), Amblyopia is considered to be amblyopia if it is 5/10 (in fraction) and is amblyopia if the difference between the eyes is more than 2 lines. Ophthalmologic examinations were performed in both groups separately and the results of the examination were kept confidential in each child’s file.

Ethical considerations

The study was approved by the ethics committee, Babol University of Medical Sciences, Babol, Iran 18-08-2019. Oral informed consent for data acquisition was provided by the parents. No financial compensation was provided. Eyelid and conjunctivitis, corneal inflammation, blurred vision, irritation, and increased sensitivity to light are important side effects of Cyclopentolate eye drops. Another rare complication of this drug is fever. The parents of the child were informed and trained in this study.

Results

Of the 180 children (90 children in the case group and 90 children in the control group), strabismus was seen in both control and case groups in 6 children. In the case group, of the 6 children with strabismus (isotropic), 2 children had right eye strabismus, 2 children left eye, and 2 children had alternative strabismus. The incidence of strabismus in the two control and case groups was not significantly correlated. (P = 0.885) [Table 1].

In the children of the case group, there were 3 children with amblyopia (2 children with right eye amblyopia who had both strabismus and hyperopia, and 1 child with left eye amblyopia who had strabismus and left eye myopia), But in control group 11 children had amblyopia (4 children with right eye, 4 children with left eye, and 3 children with both eyes). The incidence of amblyopia in the two control and case groups was not significant. (P = 0.119) [Table 2].
Refraction errors were observed in the case group in 15 children (16.67%), whereas in the control group, 27 children (30%) were observed. Refraction errors in the case group included: 2 myopia (-4.00 and -3.00), 9 hyperopia (+5.00 to +3.00) and 4 astigmatism (-2.50 to -2.00). Refraction errors in the control group included 3 myopia (-7.00 to -3.00), 20 hyperopia (+7.00 to +3.00), and 4 astigmatism (-2.00). There was no significant relationship between refractive errors in the control and case groups. (P = 0.144)

Right eye visual acuity in the case group had 81 children score greater than 0.9. In the control group, 71 children had a score greater than 0.9. Right eye visual acuity in the case and control groups was not significantly correlated. (P = 0.065) [Table 3].

Visual acuity of the left eye in the case group was 85 children with a score greater than 0.9 and in the control group 73 children with a score greater than 0.9 were reported. Visual acuity of the left eye was significantly correlated in the case and control groups. (P = 0.028). In the case group of 90 examined children, 62 infants had some degree of ROP during infancy while 28 children did not have ROP. The control group at infancy was not significantly different. Of the 6 children with strabismus, 1 had left eye amblyopia. Of the 62 children with a history of ROP, 2 had amblyopia in the right eye and 1 in the left eye. No significant relationship was found between ROP and amblyopia in the case group. (P = 0.496) [Table 4].

In the case group of 28 children with no history of ROP, none had strabismus. But of the 62 children with a history of ROP, 6 had strabismus. There was no significant relationship between ROP and strabismus in the case group. (P = 0.088).

In the case group of 28 children with no history of ROP, none had amblyopia. But of the 62 children with a history of ROP, 2 had amblyopia in the right eye and 1 in the left eye. There was no significant relationship between ROP and amblyopia in the case group. (P = 0.496)

In the case group of 28 children with no history of ROP, 1 child had hyperopia (+3.00). Of the 62 children with a history of ROP, 2 children were with myopia (-4.00 and -3.00), 8 children were hyperopia (+5.00 to +3.00), and 4 children with astigmatism (-2.50 to -2.00). There was no significant relationship between ROP and refractive errors in the case group. (P = 0.156) [Table 5].

In the case group of 28 children with no history of ROP, all had right eye visual acuity equal or more than 0.9, while in 62 children with a history of ROP, 53 children had a visual acuity equal or more than 0.9. No significant correlation was found between ROP and right eye visual acuity in the case group. (P = 0.211)

In the case group of 28 children with no history of ROP, all had left eye visual acuity equal or more than 0.9, while in 62 children with a history of ROP, 57 children had a visual acuity equal or more than 0.9. No significant correlation was found between ROP and visual acuity in the left eye. (P = 0.495)

In the control group of 84 children who did not have strabismus, 4 children had right eye amblyopia, 3 children had left eye amblyopia, and 3 children had amblyopia in both eyes. These children all had hyperopia (8 children) and myopia (2 children). Of the 6 children with strabismus, 1 had left eye amblyopia. There was no significant relationship between strabismus and
In this study, we showed that the children in the case group showed a higher incidence of hyperopia (42.2%). Strabismus was also a common finding in children with ROP. A positive relationship between strabismus and amblyopia with abnormal structure was found in one or both eyes at the age of 6 years. In the study was shown that amblyopia is a risk factor for strabismus at any time before age 6. They stated that they did not evaluate the association between amblyopia diagnosis and the onset of strabismus. In addition, they failed to show whether amblyopia contributed to strabismus or whether strabismus contributed to amblyopia. In this study, the incidence of strabismus was 6.67% in all children. Strabismus and amblyopia were not a common finding in children with ROP. We were able to show that there was a relationship between strabismus and amblyopia in the case group. In other words, strabismus has contributed to the development of amblyopia. Our study showed that strabismus at any time before 6 years of age is a risk factor for amblyopia.

In a study by Chin-Jo Hsieh et al., they showed that premature infants with severe ROP had significantly more refractive errors than infants with mild ROP and without ROP. There was no significant difference in the incidence of refractive errors at the age of 2 years in patients without ROP, mild ROP, and in the control group. They affirmed future research on preschoolers and school age is necessary to confirm long-term outcomes of refractive errors. In this study, we showed that the children in the case group with a history of ROP had more severe refractive errors (22.58%) than children without ROP (3.57%). Incidence of refractive errors among children without ROP, children with ROP and control group were very different. In our study there was a significant relationship between refractive errors and amblyopia in the control group (P < 0.001).

### Table 6: Relationship between refractive errors and amblyopia in the control group

| Refractive Errors | Control Group NO (%) | Right (% | Left (%) | Both Eyes (%) | Total (%) |
|-------------------|-----------------------|----------|----------|---------------|-----------|
| No                | 63 (100%)             | 0 (0%)   | 0 (0%)   | 0 (0%)        | 63 (100%) |
| Myopia            | 2 (66.7%)             | 0 (0%)   | 0 (0%)   | 1 (33.3%)     | 3 (100%)  |
| Hyperopia         | 10 (50%)              | 4 (20%)  | 4 (20%)  | 2 (10%)       | 20 (100%) |
| Astigmatism       | 4 (100%)              | 0 (0%)   | 0 (0%)   | 0 (0%)        | 4 (100%)  |
| Total             | 79 (87.8%)            | 4 (4.4%) | 4 (4.4%) | 3 (3.3%)      | 90 (100%) |
| P                 |                       |          |          | 0.001         |           |

Discussion

This study showed a significant relationship between strabismus and amblyopia in the case group (P < 0.001). There was no significant relationship between strabismus and amblyopia in the control group (P = 0.392). There was a significant relationship between refractive errors and amblyopia in both the control group and the case group (P < 0.001). In the case group of the 90 children, 62 children had ROP, and 28 children had no history of ROP. There was no significant relationship between ROP and visual impairment including amblyopia, strabismus, refractive errors, and visual acuity. This study shows that there is a relationship between strabismus and amblyopia with prematurity. The incidence of strabismus in both groups was equal (6.67%). The incidence of amblyopia was higher in the control group (12%), the incidence of amblyopia was 3.33% in the case group, the incidence of refractive errors was higher in the control group (30%), the incidence of refractive errors in the case group was 16.67%. Right eye visual acuity of more than 0.9 was reported in the case group of 81 children (90%) while in the control group there were 71 children (78.89%). Left eye visual acuity of more than 0.9 was reported in the case group of 85 children (94.44%) while in the control group of 73 children (81.11%).
In our study refractive errors were found in 23.33% of children, strabismus in 6.67% of children and amblyopia in 7.78% of children. There was no significant relationship between strabismus and ROP (P = 0.008), and no significant relationship between refractive errors and ROP (P = 0.156).

In the study of Hellgren et al., at the age of 6.5 years, 37.9% of the case group, and 6.2% of the control group had visual impairment. Strabismus (17.4%) and refractive errors (29.7%) were found in the case group. In the control group, refractive errors were 5.9%, and strabismus 1%. In their study, treatment-requiring ROP was a strong impact factor on visual impairment and strabismus, but not on refractive errors, as a whole.[1] In our study, at the age of 5–6 years, 26.67% of case group and 48.89% of control group had visual impairment. Amblyopia 3.33%, strabismus 6.67%, and refractive errors 16.67% were found in the case group. In the control group, amblyopia was reported 12.22%, strabismus 6.67%, and refractive errors 30%. In the present study, visual impairment were higher in the control group than in the case group.

**Conclusion**

The high rate of visual impairment in the control group of children who were all without ROP should emphasize the need for careful visual examination of children at an early age and remind parents of the importance of visual impairment and its follow-up. The relatively low incidence of visual impairment in the children in the case group, all of whom were premature, with or without ROP, may indicate timely treatment and neonatal follow-up. Also, children in the case group who had a history of ROP were treated with Avastin, which has fewer side effects than other treatment modalities and these children had less visual impairment in this study. However, to date, there are more therapeutic approaches in infants who need ROP treatment and their benefits and disadvantages have been studied.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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