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TO EVALUATE REFRACTIVE STATUS AMONG THE BABIES TREATED WITH EITHER LASER PHOTOCOAGULATION OR RECEIVED INTRAVITREAL RANIBIZUMAB INJECTION FOR THE TREATMENT OF ROP

Ophthalmology

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ABSTRACT

PURPOSE: To evaluate refractive status among the babies treated with either laser photocoagulation or received intravitreal ranibizumab injection for the treatment of ROP.

METHODS: This is an institution based retrospective cohort study, in a tertiary eye care centre of Kolkata. Total of 90 preterm infants with ROP were classified into three groups A, B and C respectively. In each group, there were 30 babies. All babies of group A, were termed delivered with more than 2.5 kg weight. In group B, all babies underwent laser photocoagulation therapy for type1 ROP. In Group C, all babies received intravitreal ranibizumab injection for type 1 ROP. All babies were followed up at 1st, 3rd, and 6th months of their respective age. In each visit, Indirect Ophthalmoscopy and cycloplegic refraction were performed.

RESULTS: The final refractive error (mean spherical equivalent) after 6 months in three groups were +0.77, -1.83 and -0 .525 respectively.

CONCLUSION: A significant refractive error (myopia) developed in two groups B and C. Myopic changes was more with laser photocoagulation group infants at 6 months as compared to intravitreal Ranibizumab treated group. Our study revealed that myopia was influenced by laser photocoagulation than intravitreal Ranibizumab. This myopic change begins before the age of 6 months age.

KEYWORDS

INTRODUCTION: Retinopathy of prematurity (ROP*)* is a widely recognized cause of visual impairment in premature infants that occurs due to abnormal retinal vasculature at the boundary of vascularized and avascular peripheral retina . Advancement in infant healthcare has led to an increased survival of prematurely born infants in the middle income countries. Preterm infants are at risk for cerebral palsy, developmental delays, and hearing problems. Ophthalmic complications of prematurity includes refractive error, strabismus, amblyopia, abnormal retinal vessels or ROP, visual loss due to reduced development of visual cortex, cortical visual impairments, and some late onset problems such as glaucoma, retinal detachment, and phthisis bulbi. Blencowe et al estimated that every year 32000 neonates become blond or developed severe visual impairment due to ROP worldwide[1]. Incidence of babies with any form of ROP ranges from as low as 2.3% to as high as 47.1%.[2,3] **Gilbert et al**. in 2005, reported the prevalence of ROP related blindness in India to be approximately 0.2% of the worldwide burden[4]. It is well established that prematurity, low birth weight and ROP increases the risk of myopia[5,6]. Laser photocoagulation and anti VEGF are considered as main treatment options. Both act by ablating abnormal retinal tissue and stop release of angiogenic factors. Long term optical status and refractive outcome in children with ROP who underwent laser treatment is well known to us. Therefore aim of this study is to evaluate the short term refractive error development in neonates with regressed ROP including those with history of laser photocoagulation or intravitreal Ranibizumab by retrospective cohort study in pre-term infants with gestational age less than 37 weeks and birth or weight less the 2500gm with no history of CVS ,CNS or any other organic eye diseases except for ROP.

METHODS: It was an institution based retrospective interventional study of babies having gestational age <37 wks, birth weight<2500 gms who underwent laser photocoagulation (LPC) and anti VEGF injection intravitreally. The study was approved by the institutional ethics committee. We reviewed the case records of all infants who visited the pediatric ophthalmology clinic between 1st January, 2018 and 30th June, 2018, with a history of LPC and intravitreal injection of Ranibizumab for ROP. We excluded patients with gestational age ≥ 37 weeks; birth weight ≥ 2500 gms; any other organic eye diseases except for ROP, uncooperative parents or legal guardians, not giving consent to be examined, refractive media opacity, pupils that fail to dilate after, other factors causing refraction difficulty, any CNS abnormality, Cerebral Palsy. Informed consent was signed by Parent's or legal guardian's. Data collected includes gestational age of baby, stage of ROP involvement, presence of APROP, plus disease, unilateral or bilateral treatment, and the spherical equivalence at 1 month, 3 months, and 6 months of age. **LASER TREATMENT (LPC)**- Laser photocoagulation was advised for infants who developed either high risk prethreshold or threshold disease as per the Early Treatment for ROP (ETROP) classification or if APROP was observed. Before laser treatment, the pupils were dilated with 1 drop of Cyclopentolate (0.5%), Tropicamide (0.4%) & Phenylephrine HCL (2.5%) instilled into eyes thrice at 15 minutes interval. LPC was performed using 810nm transpupillary diode laser with + 28D lens under topical anesthesia (Proparacaine hydrochloride 0.5%) using an infant wire speculum & sclera indentation under the supervision of neonatologist in the respective NICUs only. Laser parameters were titrated to achieve pale white burns. The avascular retina beyond the ridge right upto ora serrata was ablated using near- confluent medium -intensity burns leaving a less than half burn width apart over one or two session in both eyes. **INTRAVITREAL RANIBIZUMAB INJECTION (0.625 mg)** 0.025ml was administered under aseptic condition given in the operation theater under topical anesthesia ,using0.5% proparacaine hydrochloride drops, application of providone -iodine to the conjunctival sac, and after periocular skin is prepared with chlorhexidine gluconate 2%, a periocular drape and speculum applied given in the operating room at 1 mm posterior to the limbus and utilizing a 32 –gauge needle. Each of the infants receving Intravitral Ranibizumab was re-examined on day 1 and then 1 week and 2 weeks post administrationwas administered under aseptic condition in operation theatre. All children who had undergone laser therapy were reviewed periodically until all signs of thresholds were regressed & follow up was terminated once retinal vascularisation has proceeded to retinal periphery in all quadrants. At presentation, and 1st, 3rd, 6th month after treatment, all infants underwent a complete ophthalmological evaluation including dynamic refraction. Refractive error was converted to spherical equivalent (SE), and defined as spherical error + ½ cylindrical errors. Anisometropia was defined as the difference of SE between the eyes of ≥ 1.5D. The stage and severity of ROP were classified according to the international classification of ROP. The indication for laser treatment was as per the Early Treatment for ROP Cooperative group (ET-ROP).

RESULTS: ROP was diagnosed in 60 babies. A total of 30 preterm babies (Group B) had received conventional laser treatment. Rest 30 (Group C) babies received intravitreal anti VEGF Ranibizumab injection. Another 30 babies were unexposed to either laser or anti

VEGF injection in Group A, which was considered as a control. There were 18 male, 12 female babies in Group A and 14 male, 16 femle babies each in Group B and Goup C. In Group A, all the babies were full term (>37wk); whereas in Group B, mean gestational age of babies were 25.03±2.68 wk and in Group C, mean gestational age of babies were 26.27±2.61 wk. In group A, all the babies were > 2.5 kg whereas in Group B, 5 babies were in between 1.5-2.0 kg and 25 babies were < 1.5kg. In Group C, 7 babies were in between 1.5-2 kg and 23 babies were < 1.5 kg.

Spherical Refractive Status : One way ANOVA showed that there was significant difference in refractive error the patients of the three groups at 1month, 3month and 6 month follow up ($p<0.001$).(table 1)

Cylindrical Refractive Status : However, one way ANOVA showed that there was no significant difference in refractive error the patients of the three groups at 1 month ($p=0.884$), at 3 month ($p=0.598$) and at 6 month ($p=0.942$). (table 1)

Table-1 : Comparison of Refractive Error of the babies of the three groups at different follow up

Refractive error At different Follow up	GROUP A			GROUP B			GROUP C		
	Mean± SD	Median	Range	Mean±SD	Median	Range	Mean±SD	Median	Range
Refractive Error at 1 month (spherical)	1.75±1.71	1.75	-5.00 – 4.50	0.23±1.62	0.5	-4.00- 5.00	2.40±1.29	2.5	-1.00- 4.50
Refractive Error at 1 month (cylinder)	0.48±2.00	1.125	-4.00- 2.50	0.01±1.32	0.5	-1.50- 1.00	1.00±0.01	1.00	1.00- 1.00
Refractive Error at 3 month (spherical)	1.31±1.76	1.5	-4.50- 4.50	-0.78±1.52	-0.5	-5.00- 2.00	0.99±1.18	1.5	-2.00- 2.50
Refractive Error at 3 month (cylinder)	-0.83±251	-1.5	-4.00- 1.75	0.75±1.69	0.75	0.75- 0.75	0.50±0.00	0.5	0.50-0.50
Refractive Error at 6 month (spherical)	1.22±1.66	1.5	-5.00- 4.50	-1.58±1.69	-1.75	-0.65- 2.00	-0.18±0.91	-0.375	-3.00- 1.50
Refractive Error at 6 month (cylinder)	-0.90±2.29	-1.5	-4.00- 2.50	-0.50±1.00	-0.5	-1.50- 0.50	-0.69±0.55	-0.5	-1.50- 0.25

Refractive Outcome: The mean spherical equivalent was +1.99 in Group A, +0.235 in Group B, and +2.90 in Group C at 1 month follow up. The mean spherical equivalent +0.895, ─0.36, +1.24 in Group A, B, C respectively at 3 month follow up. The mean mean spherical equivalent at 6 months were +0.77, ─1.83, and ─0.525 in Group A, B, C respectively. (table 2)

Table 2 : Mean Spherical Equivalent Of Refractive Errors in Three Groups at different follow up (Spherical Equivalent = Spherical +Cylinder/2DSph)

Mean Spherical Equivalent At Different follow up (DSph)	GROUP A	GROUP B	GROUP C
1month	+1.99	+0.235	+2.90
3month	+0.895	-0.36	+1.24
6month	+0.77	-1.83	-0.525

It has been observed that Group C has developed less myopia at 6 months of follow up with mean spherical equivalent of -0.525DSph compared to Group B with mean spherical equivalent of-1.83DSph.

No ocular complications such as corneal oedema , hyphema , iris burns , vitreous hemorrhage ,or cataract were noted during the photocoagulation procedure in any of the eyes. Only 1(3.3%) case of macular burn in group B noted. 3 eyes had an unfavorable outcome after laser treatment and progressed to stage 4A ROP with fovea threatening TRD requiring lens sparing vitrectomy. LPC was performed on a further six patients to treat disease recurrence. A limited number of studies in the literature report severe complication following intravitreal Ranibizumab administration including the development of macular holes, the occurrence of RRD, development of optic atrophy and the risk of endophthalmitis

DISCUSSION:

ROP which develops in pre term neonates after birth is a potentially avoidable cause of vision impairment and blindness. According to the WHO date of 2010, 3.5 million of 27 million babies born in India were premature. Many risk factors have been reported to predispose to ROP. Oxygen therapy, anemia, exchange transfusion, PCV transfusion, septicemia, enhanced ventilator support, apnea, multiple births, clinical sepsis is some important risk factors.

Various type of treatment options in ROP include Cryotherapy was amongst the first widely accepted treatment strategies for the management of ROP in 1980 .This was followed by reports of laser treatment for ROP in 1990. Not only is laser easier to administer, the final visual and structural outcomes have also shown to be better with laser as compared to cryotherapy .Various types of laser have been reported for treatment of ROP. Initially an argon laser (488-528nm) was used followed by diode laser (810nm). Results of the ETROP study established the efficacy of diode laser photocoagulation in early treatment of high-risk pre-threshold ROP[7]. The study showed reduction in unfavorable visual outcomes from 19.8% to 14.3% and unfavorable structural outcomes from 15.6% to 9%. Currently, diode laser is considered the standard of care for laser photocoagulation in ROP. However, since the definition of the role of vascular endothelial growth factor (VEGF) in the etiopathogenesis of ROP, the intravitreal injection of anti-VEGF drugs has also become a treatment option. Anti VEGF therapy is reported to allow normal vascularisation of peripheral retina[8]. As such anti-VEGF therapy has been used increasingly as a pharmacological alternative to laser therapy or along with laser therapy. The side effects of anti-VEGF drugs and the most effective dosages for ROP treatment among premature infants are still unknown, especially where retinal angiogenesis and avascular regions are concerned. Anti VEGF agents has been used as alternative option in cases with small rigid pupil, hazy media too, to small babies Zone1 [APROP/ Plus disease/ stage III]. Pars Plana Vitrectomy has been used for Advanced ROP with Retinal Detachment. Myopia is attributed to differential development of anterior segment structures rather than axial elongation. Greater lens thickness & shallow AC depth is commonly seen in preterm babies with the history of ROP than in normal term babies accounting for the myopia. Laser treated babies tend to develop more myopia compared to babies where disease regressed without intervention. Geleneck et al. described higher myopia in eyes receiving laser as compared with those receiving anti VEGF especially for Zone1 ROP[9]. Similar findings were reported by various other studies as well. Different studies have found a high incidence of myopia in patients who have been subjected to laser treatment. Ablation of the peripheral avascular retina, caused by laser treatment, leads to inflammation and scar tissue formation with a high reported incidence of refractive errors[10]. Reported mean spherical equivalent ranges from around -2 to -6 magnitudes. Occurrence of myopia as found by Shah et al for Zone1 APROP was higher than other studies[11]. Myopia observed by Anilkumar et al. was found to be associated with higher axial length, but unlike other studies, there was no association with lenticular thickness[12]. Kaur et al. found higher myopia was associated with higher lenticular thickness and axial length at 1-year postnatal age[13]. Various studies have discussed factors associated with occurrence of myopia in eyes with history of laser for ROP. The exact mechanism of its development is still controversial. This may be because most of these studies are retrospective cross-sectional studies, and lack of documentation of progression of myopia. Moreover it is difficult to ascertain whether the resultant myopia is due to severe ROP or laser. Katoch et al in their study concluded that the risk factors for myopia were due to greater numbers of laser spots, and a longer time for regression of ROP[14]. In prematurely born infants, gestational age and birth weight cannot be controlled. Only strict neonatal cases, early treatment for ROP, and timely referral can control the severity of the disease, reduce myopia, and provide a good visual outcome. Many authors have concluded myopia to be associated with ROP laser treated than laser with intravitreal anti VEGF injection, non – ROP infants, and spontaneously regressed ROP cohort. Choi et al concluded that myopia begins to appear at 6 months of age, and its severity increases with between the ages of 6 months and 3 years, and eyes with cicatricial retinopathy tended toward myopia[15]. ET ROP

findings suggested that increased myopia, in fact, is due to more severe ROP, rather than any direct effect of laser treatment. The reason for developing myopia in laser treated eyes seems to be controversial. Randomized control trials would provide more light in the unknown aspects of why myopia is common in these eyes.

CONCLUSION:

The refractive error in myopic form is very common in ROP babies treated with both laser photo coagulation or anti VEG-F injection. Laser photo coagulation is responsible for more shifts towards myopia. These myopic changes begin before 6 months of age as previously considered to be developed after 6 months of age.

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