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Outcome of Aggressive Posterior Retinopathy of Prematurity in a Tertiary Care Hospital in South India

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ABSTRACT
Objective: *The aim of this study is to assess the incidence, clinical pattern, factors associated and outcome of Aggressive Posterior Retinopathy of Prematurity (APROP) in a tertiary care hospital in South India.*
Methods: *A prospective follow up study was done by screening 1738 preterm babies with gestational age <34 weeks and or birth weight <1500 grams for a period of four years from March 2012 to February 2016. ROP of any severity was present in 412 cases of which 18 cases had APROP. Regression pattern was assessed by fundus examination at periodic intervals. Structural and functional outcome were determined at the end of one year in babies with APROP. Diode laser photocoagulation was done in all cases and additional intravitreal bevacizumab injection was given in 6 eyes of 4 babies.*
Results: *The incidence of APROP among the study population was 1.03% and among ROP cases were 4.37%. Important maternal risk factors were primigravida, multiple pregnancy and delivery by vaginal route. Significant postnatal risk factors included hyaline membrane disease and surfactant use. The mean post conceptional age of treatment was 32.2 weeks. Favourable structural outcome accounted for 90% of cases. Association of structural outcome with ROP parameters showed significance for pre retinal hemorrhage and fibro vascular proliferation. The predominant refractive error was myopia which was present in 17 eyes of which high myopia was present in 10 eyes. Strabismus was present in 8 eyes of 4 patients.*
Conclusions: *Aggressive posterior form of ROP has reasonably good structural and functional outcome if detected and treated early even with laser. Pre retinal hemorrhage and fibro vascular proliferation are associated with poor structural outcome.*
Keywords: *preterms, aggressive posterior, structural outcome, refractive error.*

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of developing retinal vessels seen in preterm newborns. Since the advent of recent developments in resuscitation and monitoring in neonatal intensive care units, and consequent improved survival rate of premature babies, retinopathy of prematurity is emerging as a significant cause of visual disability in children of developing countries like India.[1] The aggressive posterior form of retinopathy of prematurity (APROP) has the worse anatomical and functional outcome, as compared to the classic form of the disease.[2]

Laser photocoagulation is the gold standard treatment for proliferative ROP and has proven useful in reducing progression of classic ROP.[3] However, in treating aggressive posterior retinopathy of prematurity, a more severe and unusual form of ROP, laser photocoagulation often fails to stop its progression to retinal detachment even with timely and complete treatment.[4] Intravitreal injection of anti-vascular endothelial growth factor (VEGF) has now become popular in the management of severe ROP.

Materials and Methods

A hospital based prospective screening study was done for 4 years during the period May 2012 to April 2016 enrolling 1738 premature babies <1.5 kg and or <34 weeks of gestational age. Among these 412 babies developed ROP of varying severity, of which 18 babies developed APROP. The initial eye examination was conducted by 31 weeks postmenstrual age or 4 weeks chronologic age, whichever is later.[5] To enable early identification and treatment of AP-ROP, infants < 28 wk or < 1200 g birth weight were screened relatively earlier at 2-3 wk of age.[6]

Ocular examination of these preterm infants were done after dilating with 1% tropicamide and 2.5% phenyl ephrine eye drops applied ten minutes apart one hour before the examination. Indirect ophthalmoscopic examination was done using 28 D lens with the help of Alphonso speculum and scleral depressor. APROP was categorized separately from classical ROP, with the following distinguishing features: very severe "plus disease," posterior location (most commonly in zone I but also possible in posterior zone II), ill-defined or no ridge, arteriovenous shunting throughout the posterior pole and dilated tortuous vessels in a syncytial pattern.[7] The diagnosis of AP-ROP was according to the international classification of retinopathy of prematurity (ICROP, 2005)[8]. AP-ROP was defined as a flat network of neovascularization in posterior pole associated with increased dilatation and tortuosity in all 4 quadrants. Zone I was defined as a circle with the radius that extends from the center of the optic disc to twice the distance from the center of the optic disc and the central macula. Posterior zone II was defined as a circle whose radius is three times the distance between the center of the optic disc and the center of the macula. Persistent ROP was defined as the lack of adequate regression of ROP. Recurrence was defined as arrest of anterior progression of retinal vasculature with new demarcation line, ridge, or extraretinal fibrovascular proliferation, with or without recurrence of plus disease. [9]

Treatment was done within 48 hours of diagnosis with Diode laser photocoagulation (810 nm Oculight SLx, Iridex Co, LA, USA) in all cases with parameters of 200 mW power for 200 ms duration to achieve a grey white burn. The total number of burns per eye varied from 2000 to 3000, in 1 or 2 sessions. If ROP failed to regress retreatment was done one week after the initial treatment. These eyes were followed up until regression of disease. Intravitreal antiVEGF injection, (Bevacizumab) 0.625 mg in 0.025 mL, was given 1.5 to 2 mm away from the limbus, with a 30 G needle in persistent disease or recurrence. The patients were re examined the next day and then every week to monitor the regression of the disease. The parameters analyzed include, gestational age, birth weight, postconceptional age of treatment, APROP characteristics, regression, number of laser burns and sittings

needed. Structural outcome, refraction by retinoscopy, and ocular motility were assessed at the end of one year. The associated maternal and postnatal risk factors were assessed and structural outcome in association with the ROP characteristics and postnatal factors were analyzed. Structural outcome was classified as favourable and unfavourable. Favourable outcome includes (1) completion of full retinal vascularisation (2) progression of vascularisation into zone 3 without previous zone 2 disease (3) Post Conceptional age of 45 weeks without developing atleast type 2 ROP.

Unfavourable outcome according to ETROP includes[10] 1)posterior retinal fold involving macula 2) retinal detachment involving macula 3) fibrosing tissue obscuring view of posterior pole. The various retinal structural sequelae studied included narrowing of arcades, macular drag, disc drag, vitreal membranes, and presence of localized peripheral tractional detachment.

Functional outcome was analysed by doing Cycloplegic refraction, done at one year of age using atropine. Refractive errors in terms of spherical equivalence was calculated from the retinoscopy readings.[11] Emmetropia is termed as 0 to 4 dioptres and hypermetropia as > 4 diopters.[12] Myopia is classified into low myopia 0 to -3dioptres,moderate myopia -3 to -6 dioptres and high myopia > - 6 diopters.

Statistical Analysis

Quantitative variables are expressed as mean ± standard deviation and qualitative variables are expressed as percentage. Chi-square test was used to find association of structural outcome with post natal factors and ROP parameters. For all statistical interpretations, a $p<0.05$ was considered the threshold for statistical significance. Ethical clearance was obtained from the institutional ethics committee and informed consent of parents was obtained. The study conforms to the guidelines of Declaration of Helsinki. Statistical analysis was performed using SPSS version 17.0(Statistical Package for Social Sciences IBM Corp., New York, NY, USA).

Results

The incidence of APROP among the study population was 1.03% and among ROP cases were 4.37%. There was a slight male preponderance with a male female ratio of 1.25:1. Percentage distribution of the sample according to birth weight shows 55.6% cases in <1 kg , 38.9% in 1-1.5 kg and 5.6% in >1.5 kg group.12 babies were <30 weeks and 8 were between 30-32 weeks of gestational age. Among the maternal risk factors 61% were primi and mode of delivery was by vaginal route in 66.7% cases. History of infertility treatment was present in 39% cases.13 babies were born out of multiple births which consisted of one baby in quadruplets and one in triplets. Intrauterine growth retardation was present in 61% of cases.

Among the postnatal risk factors some type of respiratory distress was shown by all the babies and oxygen support was needed in all the cases. Oxygen more than seven days was given in 10 cases. 8 cases were given ventilator support and rest of the cases were on continuous positive airway pressure (CPAP).Hyaline membrane disease was present in 83.3 % cases and 66.7% needed surfactant therapy.

ROP characteristics (Table 1) showed 90% of cases with zone 1 disease. Severe plus disease was present in 83.3% cases. Characteristic fundus lesions of APROP showed pre retinal hemorrhage and fibrovascular proliferation in 8 eyes and persistant tunica vasculosa lentis in 22 eyes. The mean postconceptional age of laser treatment was 32.2 ± 1.5 weeks. 50% of APROP cases regressed with one sitting of laser. The mean number of laser spots delivered was 2829.1 ± 919.1 burns. Repeat laser was done in 50% of cases. ROP regressed well in all except 6 eyes of 4 patients at 3 months followup. Additional intravitreal bevacizumab injection was given in these patients.

Table:1 Percentage distribution of the sample according to ROP characteristics

ROP characteristics		No: of eyes	Percent
APROP	Present	36	100.0
	Absent	0	0.0
Zone	1	32	88.9
	2	4	11.1
Plus disease	Severe	30	83.3
	Moderate	6	16.7
post conceptional age at laser treatment	29 - 32	26	72.2
	33 - 35	10	27.8
	Mean ± SD	32.2 ± 1.5	
No:of sittings	One	18	50.0
	>one	18	50.0
No: of laser spots	<=2400	16	44.4
	>2400	20	55.6
	Mean ± SD	2829.1 ± 919.1	

Association of structural outcome with post natal parameters shows significance for hyaline membrane disease (HMD) (P=0.038) and surfactant use (P =0.017). Favourable structural outcome according to ETROP [10] was present in 32 eyes (90%) including angulation of vessels in two eyes and macular drag in one eye. Anatomical outcomes without any structural sequelae were achieved in 78.1% from zone I APROP and 100% from posterior zone II APROP group (Table 2). Unfavourable structural outcome in the form of partial retinal detachment (stage IV) occurred in 4 eyes of three patients, for which pars plana vitrectomy was done. Association of structural outcome with ROP characteristics shows significance for pre retinal hemorrhage and fibro vascular proliferation (p=0).(Table2)

Table :2 Association of structural outcome with ROP parameters

		Favourable		Others		χ2	P
		Count	Percent	Count	Percent		
Zone	1	25	78.1	7	21.9	1.09	0.297
	2	4	100.0	0	0.0		
Plus disease	Severe	25	83.3	5	16.7	0.89	0.346
	Moderate	4	66.7	2	33.3		
Pre retinal hemorrhage	Present	3	37.5	5	62.5	12.17**	0.000
	Absent	26	92.9	2	7.1		
Fibro vascular proliferation	Present	3	37.5	5	62.5	12.17**	0.000
	Absent	26	92.9	2	7.1		
Tunica vasculosa lentis	Present	16	72.7	6	27.3	2.21	0.137
	Absent	13	92.9	1	7.1		
Post conceptional age of laser treatment(wks)	29 – 32	20	76.9	6	23.1	0.79	0.375
	33 – 35	9	90.0	1	10.0		
Treatment	Laser	26	86.7	4	13.3	4.29*	0.038
	Laser+intravitreal bevacizumab	3	50.0	3	50.0		
No of sittings	One	16	88.9	2	11.1	1.6	0.206
	More than one	13	72.2	5	27.8		
No: of laser spots	<=2400	14	87.5	2	12.5	0.89	0.346
	>2400	15	75.0	5	25.0		

**: - Significant at 0.01 level, *: - Significant at 0.05 level

Functional outcome was normal in 77.8% cases. Strabismus was present in 8 eyes of 4 patients of which 2 babies had exotropia and 2 had esotropia. The predominant refractive error was myopia in 17 eyes, of which high myopia was present in 10 eyes. Astigmatism of more than one dioptre was present in 55.6% cases. (Fig. 1)

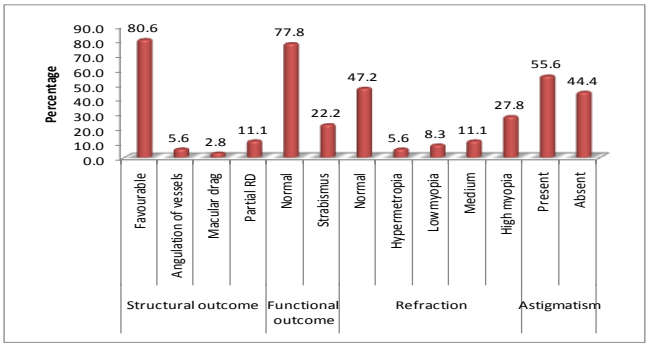

Fig:1 Percentage distribution of the sample according to outcome

Association of structural outcome with post natal parameters shows significance for hyaline membrane disease and surfactant treatment. (Table 3)

Table: 3 Association of structural outcome with post natal parameters

		Favourable		Others		χ^2	p
		Count	Percent	Count	Percent		
Congenital pneumonia	Present	12	85.7	2	14.3	0.39	0.533
	Absent	17	77.3	5	22.7		
Surfactant	Present	22	91.7	2	8.3	5.67*	0.017
	Absent	7	58.3	5	41.7		
Oxygen duration	4 -7 days	15	93.8	1	6.3	3.2	0.074
	>7 days	14	70.0	6	30.0		
Blood transfusion	Present	17	85.0	3	15.0	0.57	0.451
	Absent	12	75.0	4	25.0		
HMD	Present	26	86.7	4	13.3	4.29*	0.038
	Absent	3	50.0	3	50.0		
O2	CPAP	14	70.0	6	30.0	3.2	0.074
	Ventilator	15	93.8	1	6.3		

*: - Significant at 0.05 level

Discussion

Incidence of APROP among all the ROP patients were 4.37% which was slightly higher when compared to Gunn et al which had 2.5%.[13] There was a slight male preponderance similar to Shah et al [14] and in contrast to Gunay et al.[15] The mean birthweight was 990 grams and the mean gestational age was 29 weeks, which was slightly higher compared to other studies.[15] Similar to our study lower gestational age and birth weight are associated with worse prognosis.[16] The incidence of zone 1 changes were more when compared to a study by Sanghi et al [17] in which out of 29 eyes, 10 (34.5%) had zone 1 and 19 (65.5%) had posterior zone 2 disease. The mean age of laser treatment, number of burns and time for regression were similar to other studies.[17]

Intrauterine growth restriction and chorioamnionitis were associated with development of APROP in other studies.[18] Despite early laser photocoagulation, the favorable outcome rates for APROP vary from 71% to 84%. [7][17] Preretinal hemorrhages and new-onset fibrovascular traction especially after laser is associated significantly with development of retinal detachment.[19]

In the aggressive posterior retinopathy of prematurity (APROP), the group for early treatment of ROP (ET-ROP)[10] reported 15% unfavorable functional outcome and 10% unfavorable structural outcome with laser, due to the development of retinal folds, retinal detachment, and retrolental fibroplasia. Over the last years, the intravitreal injection of anti-vascular endothelial growth factor (VEGF) has become increasingly popular in treatment of ROP. Mintz-Hittner published the first prospective, controlled, randomized trial that proved a significantly lower recurrence rate of ROP following intravitreal bevacizumab (IVB), compared with laser photocoagulation, especially in zone I ROP.[20] Statistically significant higher APROP regression rate after IVB, was present as compared to laser photocoagulation.[21]

Myopia was the predominant refractive error and was present in 47.2% cases of which high myopia constituted about 27.8 % cases similar to other studies.[14] [22] Most preterm infants have with the rule astigmatism[23] similar to our study. Gunay demonstrated significantly higher rates of strabismus following laser treatment compared to IVB monotherapy.[15]

Conclusion

Extremely low birth weight, low gestational age, zone 1 disease, preretinal hemorrhages and fibro vascular proliferation are significant factors associated with poor structural outcome in aggressive posterior ROP. The incidence of refractive errors like high myopia is more common in APROP than classic ROP.

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