http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v10i10.23

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Prophylactic Propranalol In Prevention of Retinopathy of Prematurity in Premature Neonates

Authors
Dr Bismilla Mansuri[1*], Dr Shaista Parween[2], Dr Subhash Valinjkar[3]
[1]M.D Paediatrics Junior Resident, Department of Paediatrics, Grant Government Medical College, Mumbai
[2]M.D Paediatrics Junior Resident, Department of Paediatrics, Grant Government Medical College, Mumbai
[3]M.D Paediatrics, Associate Professor, Department of Paediatrics, Grant Government Medical College, Mumbai
*Corresponding Author
Dr Bismilla Mansuri

Abstract
Retinopathy of prematurity (ROP) is important cause of preventable blindness and ocular disabilities in premature neonates.
Objectives: *The current study is done to determine the role of prophylactic propranalol in prevention of retinopathy of prematurity in premature neonates (25-36 wks) and to compare the incidence of ROP in premature neonates receiving oral propranalol in those not receiving oral propranalol.*
Material and Methods: *This was a single centric observational prospective comparative study. The sample size of this study was 100, divided into 2 groups A and B. Group A = neonates in whom propranalol was given and Group B = neonates in whom propranalol was not given. Neonates in Group A were given oral propranalol 0.5mg/kg/day 12hourly for 14 days. ROP screening was done after 4 weeks of post menstrual age.*
Results: *Progression of ROP was significantly less (16%) in neonates who were given propranalol (Group A) prophylactically as compared to neonates in whom propranalol was not given (36%) Group B. Majority of neonates in Group A required no intervention (88%) as compared to those without propranalol therapy (64%) Group B.*
Conclusion: *Our study concludes that use of prophylactic propranalol reduces progression of ROP to higher stages as well as requirement of intervention.*
Keywords: *Propranalol, Neonate, ROP and Blindness.*

Introduction

Retinopathy of prematurity (ROP) was previously known as retrolental fibroplasia is a leading cause of blindness among premature neonates. It is a disorder of retinal blood vessels due to abnormal response of premature neonates retinal vasculature to prematurity and therapy for its management. There are two phases of ROP (1) An acute phase in which normal vasculogenesis is interrupted and (2) A chronic phase in which vascular membranes proliferate into the vitreous. This disorder may regress completely or leave behind a spectrum of sequelae ranging from myopia to significant visual loss caused by retinal detachment and scarring of macula as a result of the chronic phase.[(1,2)]

With the tremendous advancement in neonatology and increased survival of preterm neonates, have increased population of babies at risk of developing ROP. Premature neonates with birth weight less than 1500 grams and gestational age below 34 weeks constitute about 1.9% of total live births in a tertiary level neonatal care unit in India [(1)] Incidence and severity of ROP increases with decreasing birth weight and gestational age. Thus 9 out of 10 neonates with birth weight less than 750 grams or less will develop ROP while only

4.7 out of ten in a birth weight group of 1000-1250 grams will develop ROP.[3] Similarly, the incidence of ROP reported in gestational age groups of 24-27weeks, 28-31weeks, and 32-35weeks and above 36 weeks is 89%, 63%, 26%, and 19% respectively. [3] A study from the Indian subcontinent done by the Vision Research Foundation quotes an incidence of 38% for a birth weight less than 1500 grams criteria.[4]

With the increasing number of neonatal units across the country the total number of neonates requiring screening and treatment for ROP is likely to increase .In the absence of an effective screening strategy an increasing number of premature neonates who could have been successfully managed may turn irreversibly blind. The social and economic burden of childhood blindness as a result of ROP is immense. There are several compelling reasons to have a screening programme for ROP. The premature neonate is not born with ROP and retinal disease is not present at birth. Each such neonate has a potential for normal vision even if retina is immature at birth. Secondly the grief and personal tragedy for the family is tremendous, besides the economic burden of such childhood blindness. There are indefensible legal repercussions should an infant develop ROP and retinal detachment but had not received eye examination.

A number of risk factors have been put forward as playing a role in development of retinopathy of prematurity like multiple gestation, anemia, blood transfusion, hyperbillirubinaemia, phototoxicity, sepsis, respiratory distress syndrome, hyaline membrane disease, oxygen administered, surfactant, exchange transfusion, cyanotic heart diseases, PDA, intraventricular hemorrhage besides maternal factors and complications of pregnancy. Early identification of neonates with these risk factors and subjecting them to timely screening helps to provide an opportunity for effective treatment.[2, 4]

Vascular endothelial growth factor (VEGF), a key factor in the pathogenesis of ROP, is essential for retinal blood vessel development and growth.[5] Inappropriately high retinal and vitreal VEGF levels seem to be important in the development of ROP. Retinopathy of prematurity proceeds in a biphasic fashion. In the first phase, VEGF levels are reduced by a relatively hyperoxic environment, resulting in vessel obliteration. In the second proliferative phase, starting around 32 weeks' postmenstrual age (PMA), VEGF levels are elevated as a result of relatively hypoxic circumstances.[6-8] This leads to neovascularization in the retina with development of aberrant blood vessels from resident vasculature.[8]

Standard treatment for individuals at advanced stages of ROP includes laser photocoagulation and cryotherapy. Despite the overall treatment success of such retinal ablation therapy, ROP has remained a major cause of potentially avoidable blindness and visual impairment among children worldwide, indicating the importance of new strategies for prevention and treatment of this disease. A recently developed therapeutic approach for ROP focuses on use of beta- adrenergic blocking agents (beta- blockers), given that beta- 2 receptors are involved in the regulation of VEGF and IGF- 1 levels and play an important role in the pathogenesis of several neovascular retinal diseases.[9]

Beta- blockers, most commonly propranolol, has been suggested both for early prevention of ROP and for treatment of existing ROP in preterm neonates. Propranolol has been used for treatment of infantile haemangioma, for which it is thought to act by reducing VEGF levels.[10, 11] Similarities between regulation of growth of infantile haemangiomas and development of ROP have been postulated[12], and support the hypothesis that propranolol could be effective in the treatment of ROP due to beneficial effects on retinal neovascularization. Propranolol is used in children to treat a variety of diseases, including hypertension, cardiac arrhythmia, obstructive heart disease, thyrotoxicosis and migraine headache, and is generally well tolerated.[13]

Therefore, the present study was conducted to assess the effect of propranolol in the management of retinopathy of prematurity among enrolled premature neonates.

Materials and Methods

In the present study entitled, prophylactic propranolol in prevention of retinopathy of prematurity in premature neonates, we applied following methodology

Study Design

This was a single centric, observational, prospective, comparative study

Study Site

The study was conducted in department of pediatrics (Neonatology) of a tertiary care hospital.

Study duration

The study was conducted for a period of 18 months from February 2018 to September 2019

Study population

All neonates with gestational age between 26 weeks to 35 weeks admitted in NICU.

Sample size

100

All neonates with gestational age between 26 weeks to 35 weeks admitted in NICU were enrolled in the study.

The enrolled neonates were divided in two groups

Group A (n=50): Neonates in whom Propranolol was given.

Group B (n=50): Neonates in whom Propranolol was not given.

Methodology

Ethical Considerations

The study was initiated after obtaining approval from the institutional ethics committee and department of pediatrics. A written informed consent was taken from the parents/guardian after the babies were stable and ready for enrolment into the study.

Selection Criteria

Participants were selected based from the following selection criteria

Inclusion Criteria

1. All neonates with gestational age between 26 weeks to 35 weeks admitted in NICU.
2. Neonates who are hemodynamically stable.
3. Neonates <1week old after written informed consent from parents/guardian.
4. Septic preterm neonates who become stable before 35 weeks of gestation.

Exclusion Criteria

1. Neonates with recurrent episodes of bradycardia (Heart rate < 90 bpm).
2. Neonates with atrio-ventricular block (Second or third degree).
3. Neonates with hypotension (Mean bp < gestational age of neonate in first week of life).
4. Neonates with refractory hypoglycemia (Blood glucose value < 45 mg/dl despite interventions).
5. Neonates whose parents refused to give written informed consents
6. Neonates born with congenital malformation.

Statistical Analysis

Data was recorded in a predesigned proforma and compiled in Microsoft excel version 2015 and analyzed. Descriptive statistics for quantitative variables was represented as mean +/- SD. Qualitative variables were represented as frequency & percentages. Fisher test or Chi-square test was used to test the association of columns and rows in tabular data, in case of qualitative, categorical data. Unpaired t test or Mann Whitney test was used to compare differences between two independent groups depending on the normality of distribution. Graphical representations were done wherever applicable. Level of significance was considered as $P \leq 0.05$. Software used for analysis was Graph pad prism.

Study Procedure

100 neonates who full filled the inclusion and exclusion criteria were enrolled in the study after taking written informed consent from their parents/guardian. The study was initiated after taking approval from institutional ethics committee. On the day of admission detailed history and clinical examination was taken into consideration and appropriate laboratory examinations were conducted. Gestational age was assessed by new Ballard score by a single observer to avoid inter observer variation. Neonates in Group A were given propranolol 0.5mg/kg/day 12 hrly for 14 days. This was given after diluting tablet (1 tab = 10 mg) in distilled water (10ml) and dose calculated according to baby weight, initially given through naso/oro-gastric tube and then given orally to Group A. The details were entered in a predetermined proforma. Neonates were monitored vigilantly for any side effects of propranolol till discharge from the hospital. ROP screening was done after 4 weeks of post menstrual age. The compiled data was statistically analyzed and studied.

Results

The present study was an observational study conducted in department of pediatrics of a tertiary care hospital after obtaining permission from institutional ethics committee and department of pediatrics. In this study 100 neonates with gestational age between 26 weeks to 35 weeks admitted in NICU were enrolled.

Neonates are divided in two groups for further evaluation.

- Group A: Neonates in whom propranolol was given
- Group B: Neonates in whom propranolol was not given

a) Age wise distribution (NBS score)

Table 1: Age wise distribution (NBS score)

NBS	Propranolol given Group A	Propranolol not given Group B
< 30	1	1
30-32	35	24
33-35	14	25
Average score (NBS score)	31.96 ± 0.94	32.16 ± 1.03
P value	0.18 (Mann Whitney test)	

- The average gestational age based on NBS score among enrolled neonates were 31.96 ± 0.94 weeks in propranolol group (Group A) and 32.16 ± 1.03 weeks in non-propranolol group (Group B).
- No significant difference in the gestational age was seen among neonates in two groups.
- Majority of the neonates had gestational age between 30-32 weeks in propranolol group (Group A) and 33-35 weeks in non-propranolol group (Group B)

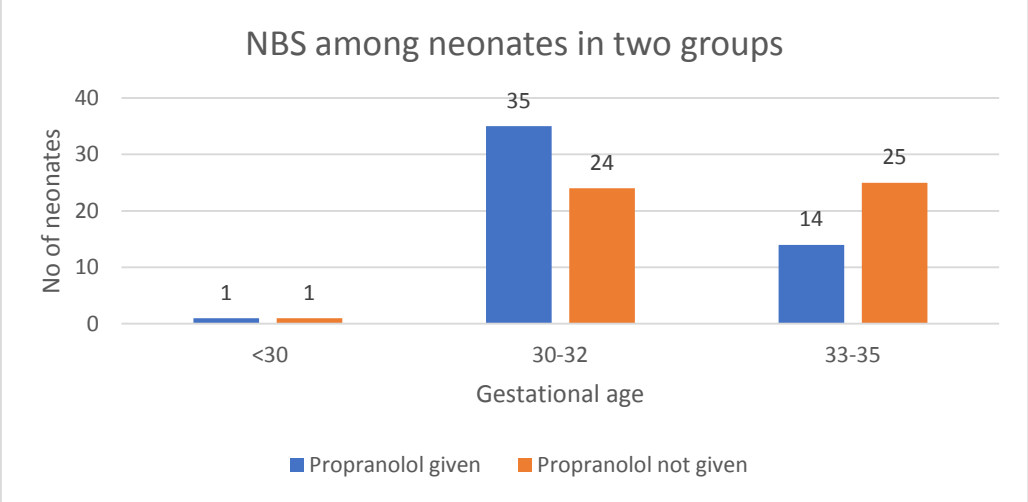

Figure 1a: Age wise distribution (NBS score)

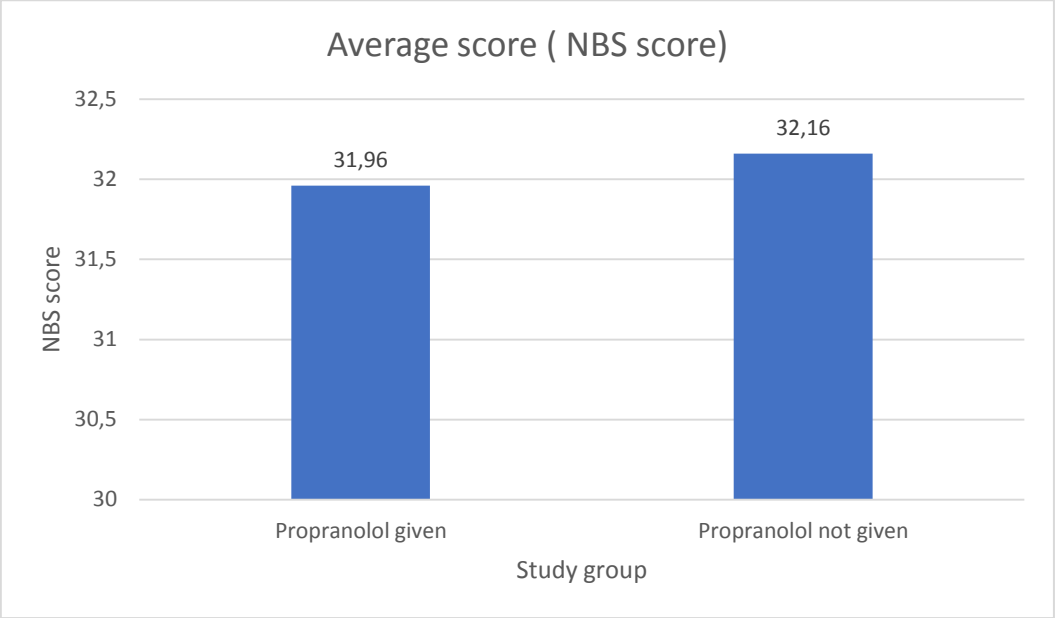

Table 1b: Average age among neonates in two groups

b) Gender wise distribution

Table 2: Gender wise distribution

Gender	Propranolol given Group A	Propranolol not given Group B
Male	31	24
Female	19	26
P value	0.22 (Fisher test)	

- Male neonates were in majority in propranolol group (Group A) (62%) and female neonates in non-propranolol group (Group B) (52%).

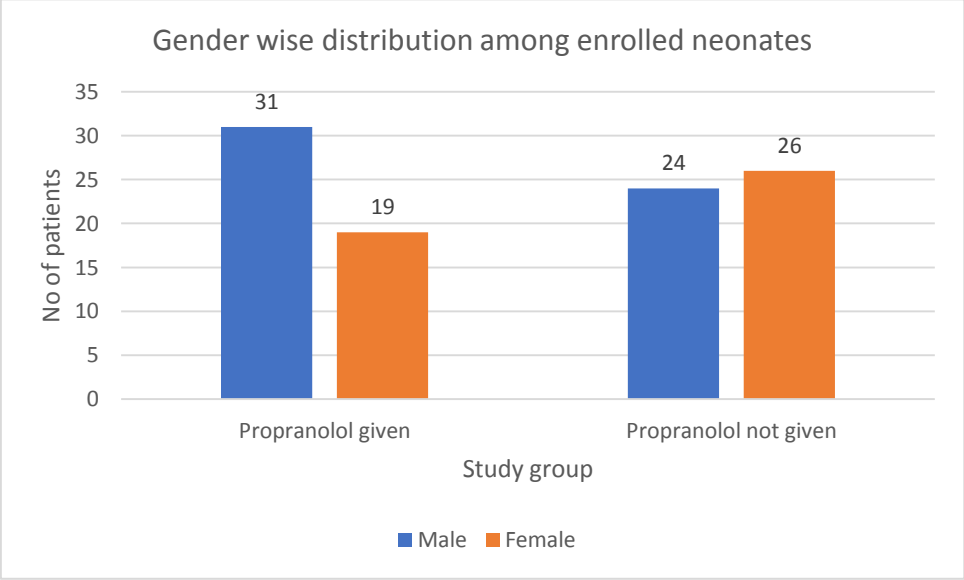

Figure 2: Gender wise distribution

c) Weight wise distribution

Table 3: Weight wise distribution

Weight (kg)	Propranolol given Group A	Propranolol not given Group B
≤1.5	22	27
1.51 to 2	25	20
>2	3	3
Average Weight (kg)	1.55 ± 0.22	1.50 ± 0.23
P value	0.14 (Mann Whitney test)	

- The average birth weight among neonates in propranolol group (Group A) was 1.55 ± 0.22 kg and that in non-propranolol group (Group B) was 1.50 ± 0.23 kg
- No significant difference was seen in the average weight among neonates in both the groups.
- Majority of the neonates in both the groups had birth weight <2kg

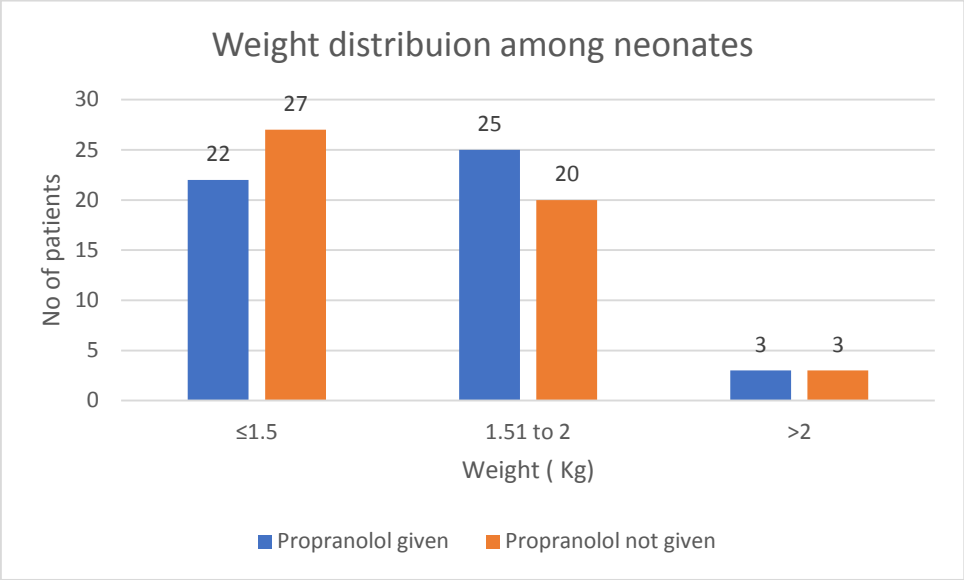

Figure 3a: Weight wise distribution

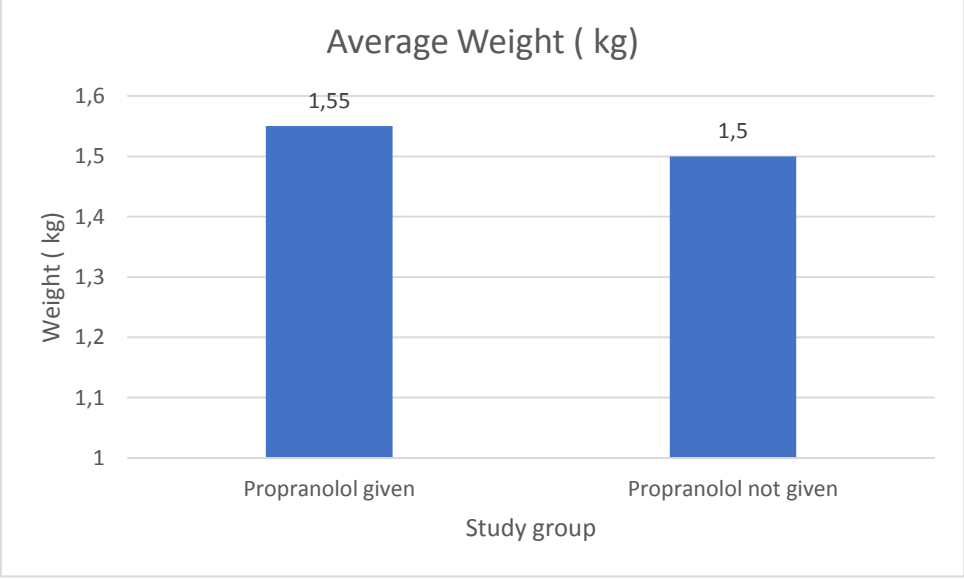

Figure 3b: Average weight among neonates

d) Mode of delivery

Table 4: Mode of delivery

Mode of delivery	Propranolol given Group A	Propranolol not given Group B
Normal vaginal delivery	44	40
LSCS	6	10
	0.41 (Fisher test)	

- Majority of neonates in both the groups were delivered by normal vaginal delivery
- No significant difference was seen in the distribution of mode of delivery

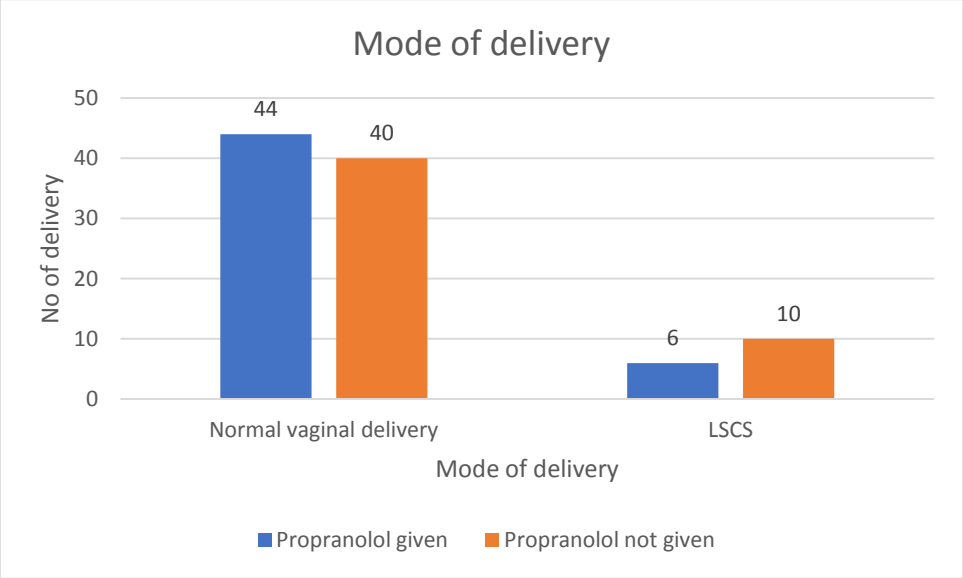

Figure 4: Mode of delivery

e) APGAR score

Table 5: Apgar score

Group	0 minutes	5 minutes
Propranolol given Group A	7.98 ± 0.55	10
Propranolol not given Group B	8.04 ± 0.49	10
P value (Mann Whitney test)	0.63	-

- No significant difference was seen in the Apgar score among neonates in two groups at 0 minutes.
- The Apgar score was 10 among neonates in both the groups at 5 minutes.

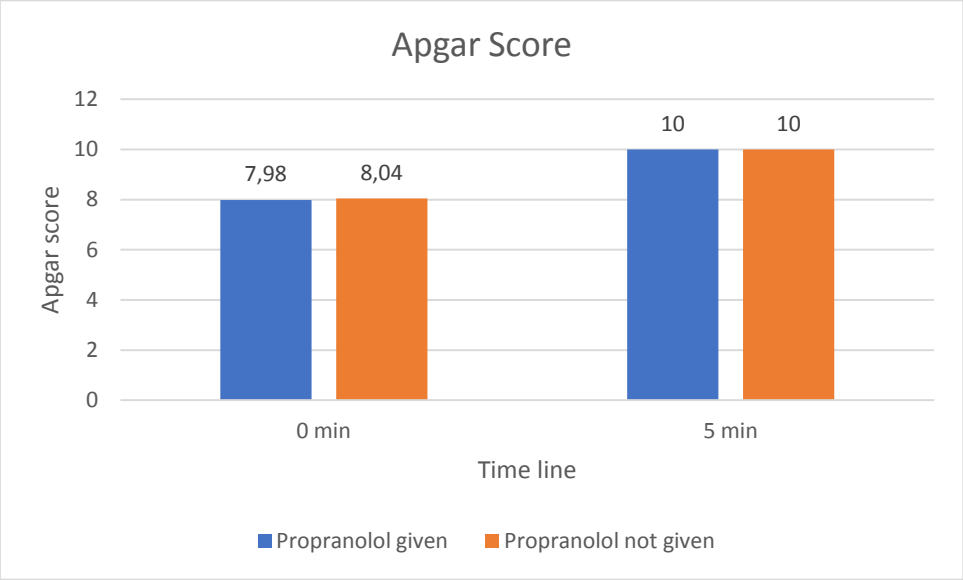

Figure 5: Apgar score

f) Oxygen delivery in days

Table 6: Oxygen delivery in days

Oxygen delivery	Propranolol given Group A	Propranolol not given Group B	P value (Mann Whitney test)
Oxygen by CPAP Bubble	2.48 ± 0.88	2.42 ± 0.64	0.97
Oxygen by Prongs	1.72 ± 0.57	1.74 ± 0.52	0.83
Oxygen by Hood	1.18 ± 0.66	1.2 ± 0.45	0.50
On mechanical ventilation	0.34 ± 1.56	0.14 ± 0.98	0.71

- No significant difference was seen in the average days of oxygenation in two groups.
- Oxygen by CPAP bubble was given for longer time in both the groups.

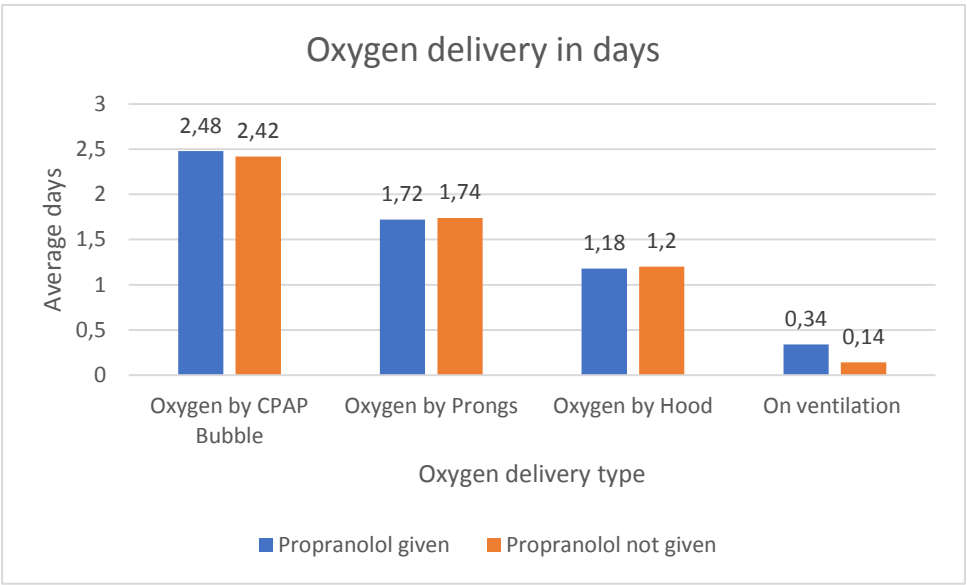

Figure 6: Oxygen delivery in days

g) ROP result

Table 7: ROP result

ROP	Propranolol given Group A	Propranolol not given Group B
Yes	8	18
No	42	32
P value	**0.03** (Fisher test)	

- Progression of ROP was significantly less (16%) in neonates who were given propranolol prophylactically as compared to neonates in whom propranolol was not given (36%) (Group B).

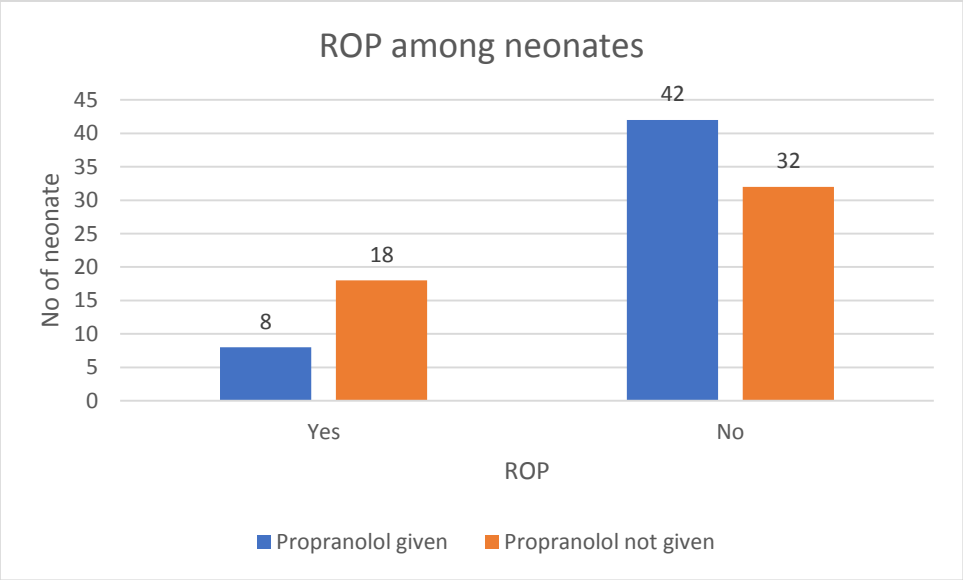

Figure 7: ROP result

Intervention given

Table 8: Intervention given

Intervention	Propranolol given Group A	Propranolol not given Group B	P value (Fisher test)
Pan retinal Photocoagulation (PRP) laser	6	15	**0.04**
PRP with Anti- VEGF	0	3	0.24
No intervention	44	32	**0.009**

- Majority of neonates in propranolol group (Group A) required no intervention (88%), as compared to those without propranolol therapy (64%) (Group B).
- PRP laser was required more in neonates without propranolol (36%) (Group B).
- The use of anti-VEGF was reported in 6% neonates in non-propranolol group (Group B).

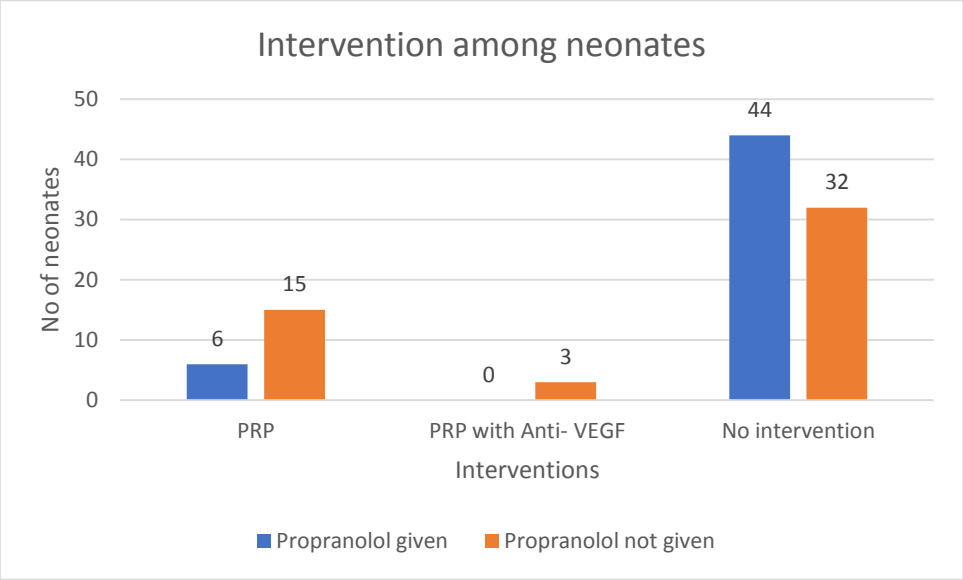

Figure 8: Intervention given

Discussion

Retinopathy of prematurity (ROP) used to be called as retrolental fibroplasia (RLF) in 1940s. RLF was the term first coined in the year 1942 by Terry [14] and was defined as a progressive disorder seen exclusively in premature infants of low birth weight, where in a fibrous tissue is formed behind the lens, resulting in blindness and severe visual impairment. When it was first described this disease was not commonly seen, and hence had little interest but 10 years later it became a major problem to all pediatricians and ophthalmologists. It now affects thousands of children worldwide.[15] Many studies were conducted worldwide since 1951 to determine the exact mechanism of this disorder. Ophthalmic literature of the past reveals, anoxia in premature babies to be the prime causative factor for the development of RLF and hence in 1952 was called as anoxic retinopathy.[16]

Globally, ROP is estimated to affect more than 50,000 infants annually. In India, every year, 500 children are estimated to become blind from ROP. [17] While ROP may cause severe visual impairments, the condition fortunately carries a good prognosis, given early screening and management. In an animal experimental model of proliferative retinopathy, it was demonstrated that the pharmacological blockade of beta-adrenoreceptors improves retinal neovascularization and blood retinal barrier breakdown consequent to hypoxia. [18]Therefore the present study was conducted to evaluate the effect of propranolol in premature neonates with retinopathy of prematurity. The average gestational age based on NBS (New Ballard Score) among enrolled neonates were 31.96 ± 0.94 weeks in propranolol group and 32.16 ± 1.03 weeks in non-propranolol group without any significant difference. Majority of the neonates had gestational age between 30-32 weeks in propranolol group and 33-35 weeks in non-propranolol group. Gestational age (GA) is considered as an independent and most important risk factor in the development of ROP with studies reporting the incidence and severity of ROP show an inverse relationship with GA. [19] TR-ROP (Turkey-ROP) study, one of the largest studies conducted in ROP, conducted on 6115 infants reported similar findings with 4964 (81%) neonates with a GA ≤32 weeks and 1151 (19%) with a GA >32 weeks.[20] Charan R[19] reported similar GA i.e. 31.49 ± 0.3 weeks as seen in our study. The average gestational age in our study was comparable to a study conducted in south India by Ahuja A[21] where the gestational age of neonates with ROP was 29.71 ± 2.64 (range 26-36) weeks. This was almost similar to study

conducted by Jasmina Alajbegovic-Halimic et al [22] where the average GA was 29.9 ± 2.9 weeks, of which the youngest neonate was at GA of 24 weeks and the oldest at 37 weeks of gestation.

Gender wise differentiation also highlighted similar findings with no difference in the neonates in two groups. But numerical difference showed, male neonates were in majority in propranolol group (Group A) and female neonates in non-propranolol group (Group B). Jasmina Alajbegovic-Halimic[22] in her study reported higher representation of female neonates (51.2%) compared to male (48.8%). Mitsiakos G [23] reported higher number of male neonates as compared to female neonates (44 vs. 33). Thus there is no gender wise differentiation in the incidence of ROP in our study and other related studies.

Similar to gestational age, birth weight is also considered as an independent risk factor for ROP. [19] The average birth weight among neonates in propranolol group (Group A) was 1.55 ± 0.22 kg and that in non-propranolol group (Group B) was 1.50 ± 0.23 kg without any significant difference. Majority of the neonates in both the groups had birth weight <2kg. Low birth weight is closely correlated to low gestational age, the respective effect on the pathogenesis of ROP and the dominance of the two factors are still unclear. Birth weight is sometimes assumed to be a quality of growth and is strongly related to infant survival. [24] Similar to our study, Wang ZH [25] in his study also reported the average weight of neonates as 1529 ± 334.20 gm (range 760-2160 gm). Charan et.al. [19], in his study reported the average birth weight ranged from 820 to 1700 (mean ± SE, 1382.84 ± 17.8) gm. This was comparable to study by Ashish Ahuja [21] where babies with ROP had a mean BW of 1285 g (SD: 0.27, range: 0.86–1.8 g). Hence it is recommended to screen low-birth weight babies to detect ROP.

Majority of neonates in our study were delivered by normal vaginal delivery in both the groups but showed no significant difference. As compared to study by Manzoni P et.al.[26], where higher incidence of neonates with vaginal delivery were reported with ROP. The study also reported that birth by vaginal delivery is independently predictive of threshold ROP requiring urgent ablative surgery in infants with birth weight <1000gm. [26] This can be because the mechanics of vaginal delivery and the pressure dynamics during the labor could be harmful for the cerebral vessels of the fetus, producing ischemia and subsequent reperfusion and/or oxidative stress with related imbalance hyperoxia–hypoxia [26], which could promote a hypoxia-induced stimulation of release and production of mediators of neoangiogenesis. This was in contrast to study conducted by Manzoni et al.[26], where 66% neonate with ROP required resuscitation at birth.

Oxygen by CPAP bubble was given for longer time in both the groups but no significant difference was seen in the average days of oxygenation in the two groups. CPAP is a non-invasive type of respiratory support which can be delivered without endotracheal intubation. It works by providing a continuous level of positive pressure to the airways which distends the alveoli, overcomes collapse and improves ventilation. Bubble CPAP is the method that is most adapted to low-resources settings.

β-adrenergic system plays a central role in the promotion of retinal neovascularization. In fact, the retinal ischemia induced by oxygen exposure promotes the release of norepinephrine, which reacts with β2 and β3- adrenoreceptors (β-AR) inducing the up-regulation of hypoxia-induced factor (HIF), vascular endothelial growth factor (VEGF) and insulin growth factor (IGF-1). [27] VEGF is a key factor in the pathogenesis of ROP, is essential for retinal blood vessel development and growth. [5] Inappropriately high retinal and vitreal VEGF levels seem to be important in the development of ROP. Beta- adrenergic blocking agents e.g. propranolol, modulates the vasoproliferative retinal process, which may reduce the progression of ROP or even reverse established ROP. Reports of use of systemic propranolol for an effective treatment of infantile

hemangioma resulted in exploration of anti-angiogenic role of propranolol in ROP. A study on oxygen-induced retinopathy in a mouse model showed that propranolol decreases VEGF overproduction in the hypoxic retina. In addition, beta-AR blockade has no effect on VEGF levels in the heart, brain or lungs, as VEGF expression in these organs is independent of hypoxia, [28] Based on these findings, the safety and efficacy of propranolol in newborns with ROP (PROP-ROP) study [29], was conducted. It evaluated safety and efficacy of oral propranolol given to preterm newborns infants having early stages of ROP. In this study, 26 preterm babies with stage 2 ROP treated with oral propranolol (0.25 or 0.5 mg/kg every 6 hrly) showed less progression to stage 3 or stage 3 plus and a 100% relative reduction of risk for progression to stage 4. However serious adverse effects like bradycardia and hypotension were observed in about 20% of infants treated with propranolol, and the study was halted due to increased mortality in the treatment arm. [29] The protective effect of propranolol was highlighted in our study where the incidence of ROP was significantly less in neonates who were given propranolol (Group A) prophylactically. Similar results were highlighted in study conducted by Korkmaz L[38] who reported neonates on propranolol therapy had better outcome and propranolol had reduced the need for laser photocoagulation significantly in such groups of neonates. Luca Filippi[39] in his prospective observational study also highlighted that the progression to ROP stage 2 or 3 plus disease was significantly lower in neonates who were on propranolol therapy. Further evaluating the stage wise usefulness of propranolol, Mehmet Adnan [40] reported, propranolol when given in the neovascularization phase of the ROP, it was found to be effective in the stage 2 (advanced stage) ROP patients but in stage 0–1 (early-stage) ROP patients, its efficacy was not sufficient. Thus, the results of our study and similar other study highlights and recommends the use of propranolol in the management of neonates with ROP.

Prior to establishment of propranolol in the management of ROP, VEGF inhibitors and laser photocoagulation were the two commonly used treatment modality. Laser photocoagulation of the peripheral retina using indirect delivery system has proved to be the gold standard, time tested and successful means of treatment since many years. Laser photocoagulation using infrared diode laser forms a portable mode of treatment and can be performed in the nursery by skilled professionals. The biggest advantage is that it can be done under topical anesthesia. Laser ablation converts the relatively hypoxic retina into anoxic, thereby reducing stimulus for new vessel formation and disease progression. The ET-ROP (Early Treatment-ROP) study from its six years analysis confirmed that eyes with type 1 ROP benefited from laser treatment at high risk pre threshold stage. [30] This failure rate of 9.6%, was better than the results shown by the CRYO-ROP (Cryotherapy for ROP) study. Laser photocoagulation has its own demerits and causes destruction of the retina amounting to significant visual field loss. Pharmacologic therapy is thus ushering a new era of ROP management.

Anti-vascular endothelial growth factor (anti-VEGF) drugs directly block the effects of VEGF, and a single intravitreal injection is less time consuming and less expensive as compared to lasers. Exceptionally successful results with anti-VEGF drugs in adult retinal vascular diseases led to its trial in pediatric retinopathy as a monotherapy as well as in combination with lasers. Intravitreal bevacizumab as an initial mono therapy was reported to cause regression of type 1 ROP in 88% cases with 9% requiring additional laser treatment and 1% requiring additional injection.[31]In our study majority of neonates in propranolol group (Group A) required no intervention in our study, the common intervention used in our study was PRP laser and anti-VEGF therapy. PRP laser is still recommended as gold standard method for treatment-requiring ROP, especially in Zone II [32] and considering the vascular nature of the disease,

anti-VEGF drug injection was considered in treatment for ROP and was mainly used for Zone I ROP, aggressive posterior –ROP (AP-ROP), and failed ROP after laser treatment. [33,34] Comparing the two therapy, the BEAT ROP (Bevacizumab Eliminates the Angiogenic Threat for ROP) trial presented favorable results of bevacizumab in Zone I but not in Zone II disease compared to laser therapy. [35] Compared to bevacizumab, recurrence rates of ROP are markedly lesser with laser, at follow-up of 5 years, thus avoiding need for periodic evaluation till complete vascularization, as required with bevacizumab. [36] The disadvantages of laser in ROP include a long learning curve, the risk of sedation, and relatively longer duration to complete the laser sitting. Anti-VEGF is a double-edged sword as the neural, vascular, lung development of these neonates is driven by the VEGF. [37] The long-term effects of these drugs in infants are unknown, and the use of off-label drugs in these infants can lead to litigation and should always be borne in mind. [37] There are very few studies in India highlighting the benefit of adding propranolol in the treatment of ROP among Indian patients, this study will help in future research in the field of ROP in India.

Our study also had few limitations

1) This was a single centric study; the result obtained from this study will not be applicable to entire nation.
2) The sample size was less in this study hence a large scale multicentric randomized study will help in evaluating the benefit of propranolol in ROP.

Conclusion

Our study concludes that use of prophylactic propranalol reduces progression of ROP to higher stages as well as requirement of intervention. This study was an attempt to highlight the usefulness of propranolol in the management of ROP. With the growing incidence of low birth weight and premature neonates, the incidence of ROP is expected to increase and the early use of propranolol will help in decreasing the progress to next stage of the disease and this study recommends the use of propranolol in the management of neonates with ROP.

References

1. Subadra J, Anand R, Kumar H, Mangat D, Rajvardhan A, Lingam G. Programme Planning and Screening Strategy in Retinopathy of Prematurity. Indian J Ophthalmol 2003;51:89-99.
2. Stephen RJ, Schachat AP, Murphy RB: Retina 2nd edition Vol II. Mosby Year Book Inc St.Louis;Baltimore;1447-1471
3. Aravind J, Devi L, Krishna R, Agarwal P. Retinopathy of Prematurity. International Journal of Science and Researc. 2018; 8(10):471-82.
4. Gopal L, Sharma T, Ramachandran S. Retinopathy of Prematurity-a study .Ind J Ophthalmol 43:59-62,199
5. Ferrara N, Davis- Smyth T. The biology of vascular endothelial growth factor. Endocrine Reviews. Endocrine Society. 1997;18(1):4- 25.
6. Asthon N, Ward B, Serpell G. Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. British Journal of Ophthalmology 1954;38(7):397- 432.
7. Chen J, Joyal JS, Hatton CJ, Juan AM, Pei DT, Hurst CG. Propranolol inhibition of β- adrenergic receptor does not suppress pathologic neovascularization in oxygen- induced retinopathy. Investigative Ophthalmology & Visual Science 2012; 53(6):2968- 77.
8. Mutlu FM, Sarici SU. Treatment of retinopathy of prematurity: a review of conventional and promising new therapeutic options. International Journal of Ophthalmology 2013;6(2):228- 36.
9. Casini G, Dal Monte M, Fornaciari I, Filippi L, Bagnoli P. The β- adrenergic system as a possible new target for

pharmacologic treatment of neovascular retinal diseases. Progress in Retinal and Eye Research 2014;42:103- 29.
10. Léauté- Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. New England Journal of Medicine 2008;358(24):2649- 51.
11. Manunza F, Syed S, Laguda B, Linward J, Kennedy H, Gholam K, et al. Propranolol for complicated infantile haemangiomas: a case series of 30 infants. British Journal of Dermatology 2010;162(2):466- 8.
12. Praveen V, Vidavalur R, Rosenkrantz TS, Hussain N. Infantile hemangiomas and retinopathy of prematurity: possible association. Pediatrics 2009; 123(3):e484- 9.
13. Drolet BA, Frommelt PC, Chamlin SL, Haggstrom A, Bauman NM, Chiu YE, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics 2013;131(1):128- 40.
14. Terry TL. Fibroblastic Overgrowth of Persistent Tunica VasculosaLentis in Infants Born Prematurely: II. Report of Cases-Clinical Aspects. Trans Am Ophthalmol Soc 1942; 40: 262-284
15. Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle-income countries. Lancet 1997; 350: 12-14
16. Szewczyk TS. Retrolental fibroplasia; etiology and prophylaxis. Am J Ophthalmol 1952; 35: 301-311
17. Gilbert C. Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev 2008; 84:77-82.
18. Smith LE, Wesolowski E, McLellan A, Kostyk SK, D'Amato R, Sullivan R, D'Amore PA. Oxygen-induced retinopathy in the mouse. Invest Ophthalmol Vis Sci. 1994; 35(1):101-11.
19. Charan R, Dogra MR, Gupta A, Narang A. Incidence of retinopathy of prematurity in a neonatal care unit. Indian J Ophthalmol1995;43:123-6
20. Bas AY, Demirel N, Koc E, Isik DU, Hirfanoglu IM, Tunc T, on behalf of the TR-ROP Study Group. Incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units. Br J Ophthalmol2018;102:1711–1716
21. Ahuja AA, V. Reddy YC, Adenuga OO, Kewlani D, Ravindran M, Ramakrishnan R. Risk factors for retinopathy of prematurity in a district in South India: A prospective cohort study. Oman J Ophthalmol 2018;11:33-7
22. Alajbegovic-HalimicJ ,Zvizdic D, Alimanovic-Halilovic E, Dodik I, Duvnjak S. Risk Factors for Retinopathy of Prematurity in Premature Born Children . Med Arh. 2015; 69(6): 409-413
23. MitsiakosG ,Papageorgiou A. Incidence and factors predisposing to retinopathy of prematurity in inborn infants less than 32 weeks of gestation. HIPPOKRATIA 2016, 20, 2: 121-126
24. Dhaliwal CA, Fleck BW, Wright E, Graham C, McIntosh N. Retinopathy of prematurity in small-for-gestational age infants compared with those of appropriate size for gestational age. 2009;94(3):193-195
25. Wang ZH, Li YY, Liu ZM. Birth weight and gestational age on retinopathy of prematurity in discordant twins in China.Int J Ophthalmology.2014;7(4):663-667
26. Manzoni P, Farina D, Maestri A, Giovannozzi C, Leonessa ML, Arisio R, GomiratoG.Mode of delivery and threshold retinopathy of prematurity in

pre-term ELBW neonates. Acta Paediatrica.2007; 96(2), 221–226.
27. Martini D, Dal Monte M, Ristori C, Cupisti E, Mei S, Fiorini P, et al. Antiangiogenic effects of β2 -adrenergic receptor blockade in a mouse model of oxygen-induced retinopathy. J Neurochem. 2011;119:1317–29.
28. Ristori C, Filippi L, Dal Monte M, Martini D, Cammalleri M, Fortunato P et.al. Role of the adrenergic system in a mouse model of oxygen-induced retinopathy: antiangiogenic effects of beta-adrenoreceptor blockade. Invest Ophthalmol Vis Sci. 2011;52:155-170
29. Filippi L, Cavallaro G, Fiorini P, Daniotti M, Benedetti V, Cristofori G et.al. Study protocol: safety and efficacy of propranolol in newborns with Retinopathy of Prematurity (PROP-ROP): ISRCTN18523491. BMC Pediatr. 2010;10:83.
30. Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL, Tung B, Redford M. Early Treatment for Retinopathy of Prematurity Cooperative Group. Final visual acuity results in the early treatment for retinopathy of prematurity study. Arch Ophthalmol. 2010;128:663-671
31. Wu WC, Kuo HK, Yeh PT, Yang CM, Lai CC, Chen SN. An updated study of the use of bevacizumab in the treatment of patients with prethreshold retinopathy of prematurity in taiwan. Am J Ophthalmol. 2013;155:150-158.e1
32. Dogra MR, Katoch D, Dogra M. An Update on Retinopathy of Prematurity (ROP).Indian J Pediatr. 2017; 84(12):930-936.
33. Darlow BA, Ells AL, Gilbert CE, Gole GA, Quinn GE. Are we there yet? Bevacizumab therapy for retinopathy of prematurity. Arch Dis Child Fetal Neonatal Ed. 2013 Mar; 98(2):F170-4.
34. Eldweik L, Mantagos IS. Role of VEGF Inhibition in the Treatment of Retinopathy of Prematurity. Semin Ophthalmol. 2016; 31(1-2):163-8.
35. Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011 Feb 17; 364(7):603-15.
36. Hwang CK, Hubbard GB, Hutchinson AK, Lambert SR. Outcomes after intravitreal bevacizumab versus laser photocoagulation for retinopathy of prematurity: A 5-year retrospective analysis. Ophthalmology 2015;122:1008-15
37. McGillick EV, Orgeig S, Morrison JL. Structural and molecular regulation of lung maturation by intratracheal vascular endothelial growth factor administration in the normally grown and placentally restricted fetus. J Physiol2016;594:1399-420.
38. Korkmaz L, Başţuğ O, Ozdemir A, Korkut S, Karaca C, Akin MA.et.al.The Efficacy of Propranolol in Retinopathy of Prematurity and its Correlation with the Platelet Mass Index. Curr Eye Res. 2017;42(1):88-97
39. Filippi L, Cavallaro G, Berti E, Padrini L, Araimo G, Regiroli G et.al. Propranolol 0.2% Eye Micro-Drops for Retinopathy of Prematurity: A Prospective Phase IIB Study. Front. Pediatr. 2019;7:180
40. Ozturk MA, Korkmaz L. The efficacy of propranolol in very preterm infants at the risk of retinopathy of prematurity: Which newborn and when?. International ophthalmology.2019;39 (9):1921-30.