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Role of Prophylactic Use of Propranolol In Prevention of ROP In Premature Neonates.

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ABSTRACT

Retinopathy of prematurity (ROP) was known as Retrolental Fibroplasia is a leading cause of blindness among Premature Neonates. ROP is disorder of retinal blood vessels due to abnormal response of Premature Neonates retinal vasculature to prematurity and oxygen therapy for its management. Incidence and severity of ROP increases with decreasing birth weight and gestational age. Early identification and timely screening of neonates with risk factors helps to provide an opportunity for effective treatment. Beta blockers, most commonly propranolol, has been suggested for early prevention of ROP and treatment of existing ROP in preterm neonates. This study is to determine the role of prophylactic Oral Propranolol in prevention of ROP in Premature Neonates (26-35weeks GA) and to compare incidence of ROP in Premature Neonates (26-35weeks GA) receiving Oral Propranolol with one receiving Placebo. This is a comparative observational study conducted in the NICU of Rural Tertiary Care Hospital. The study includes Premature Neonates 26-35 weeks of Gestational Age (GA), grouped in ratio 1:1 with one group receiving Oral Propranolol and other Placebo which were followed for ROP screening 4 weeks after Postnatal Age. There is less incidence of diagnosis of ROP in Premature Neonates receiving Oral Propranolol. Hence such Premature Neonates require less therapeutic intervention in future. Thus, Oral Propranolol is an effective treatment in the management of ROP in Premature Neonates thereby decreasing the incidence of Progression and severity of ROP.

Keywords: ROP, Premature Neonates, Oral Propranolol, Anti-VEGF, PRP laser.

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INTRODUCTION

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In both developed and developing countries, the major cause of childhood blindness is retinopathy of prematurity (ROP). ROP is a retinal vascular disease of premature infants[1]. ROP is defined as a vision-threatening disease associated with abnormal retinal vascular development at the boundary of avascular and vascularized peripheral retina[2].

In extremely premature infants and extremely low birth weight, ROP is more severe and more frequent, hence the incidence of ROP is closely related to birth weight and gestational age.[3] ROP being high among extremely low birth weight baby (ELBW), but with advances in neonatal care unit there is increase in survival of ELBW from 27% to 37% in CRYO-ROP study.[1] The incidence of ROP in USA is 68% among infants with a birth weight of 1,250kg [4.]

ROP has oxygen dependent and independent both factors.[5] Factors such as hypoxia-inducible factor 1 (HIF-1), vascular endothelial growth factors (VEGFs), insulin-like growth factor-1 (IGF-1), erythropoietin (Epo), placental growth factor (PlGF), nitric oxide (NO), adenosine, apelin, as well as the role of the sympathetic nervous system and polymorphisms of the beta-adrenoreceptors (b-ARs) are involved in pathogenesis of ROP.[6]

The supplemental oxygen is a double-edged sword as in severe ROP there is retinal detachment and distortion of retina. Both hypoxia and hyperoxia affect the levels of vascular endothelial growth factor which is essential for the development of the retinal vasculature development. Babies at risk of ROP are preterm or have associated neonatal morbidity, e.g., respiratory distress syndrome, infection, poor weight gain, and hyperglycemia.[2]

The Federal Drug Administration in the USA, a Pediatric Use Marketing Authorization by the European Medicines Agency, and Swiss Medic approved use of Oral Propranolol in infantile hemangioma. The clinical picture of infantile hemangioma and retinopathy of prematurity is similar, thus there are proven benefits of use of Oral Propranolol in ROP.[7]

In-utero environment retinal vasculature begins at 16th week and ends at 40th weeks of GA, but in preterm infants the retina has avascular areas in the first ischemic phase. This hypoxia due to ischemic phase.[5]

After the ischemic phase providing oxygen richer than uterus can cause the regression of the retinal vasculature causing oxygen induced retinopathy and in second phase hypoxia induced neovascularization.[8]

The second phase in the 2 distinct phases of pathogenesis of ROP where there is hypoxia induced up regulation of vascular endothelial growth factor and retinal neovascularization. Beta adrenergic system interfere with ROP in infants. Beta adrenergic regulate the VEGF production and retinal neo vasculature. Propranolol is a nonselective beta 1 and 2 blocker, which will block the hypoxia induced VEGF formation and retinal neovascularization.[3]

Treatment with laser affects the entire layer of the retina while with Anti-VEGF also have significant side effects.[9] Ablative therapy like laser or cryotherapy there is unfavorable visual

and structural outcomes in severe ROP.[1] Hence newer research of modalities to prevent hypoxia induced retinopathy is important hence the use of oral propranolol with its non-selective beta blocker ability is been studied in this observational study.[9]

MATERIALS AND METHOD

It is an observational comparative study was conducted in the Neonatal Intensive Care Unit in the Rural Tertiary Care Hospital from period of January 2023 to December 2023 in total 100 Preterm Neonates (Less than 35 weeks of gestation) which were then grouped into Group A of 50 cases and Group B of 50 control preterm neonate. 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. Two solution one diluted tab propranolol (1tab=10mg) in 10ml distilled water at a dose of 0.5mg/kg/day, was calculated as per weight given in two divided doses either through oral or nasogastric tube, later on orally given to group A and other dextrose 5% was given to group B for a period of 14 days. The study included Preterm Neonates of GA ≤35 weeks, ≤7 days, 26–35 weeks GA of Preterm, admitted to NICU and requiring oxygen. Exclusion criteria for the study was Preterm neonates with bradycardia, AV block, hypotension, congenital malformations, AKI and IVH. Neonates were monitored vigilantly for any side effects of propranolol till discharge from the hospital. ROP screening was done after 4 weeks of postnatal age. 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. Software used for analysis was Graph pad prism. I.

RESULTS AND DISCUSSION:

This is an Observational Comparative Study conducted in Neonatal Intensive Care Unit of Department of Pediatrics in a Rural Tertiary Care Hospital after getting permission from Institutional Ethics Committee, Department of Pediatrics and consent from parents. In the present study total 100 Preterm Neonates with the gestational age between 26 weeks to 35 weeks admitted in NICU and were divided into two groups: -

Group A: Neonates in whom Propranolol was given.

Group B: Neonates in whom Propranolol was not given (control).

Both the groups were further evaluated.

Table 1: ROP Result

ROP	Group A Preterm Neonates given Propranolol.	Group B Placebo Group

Yes	8 (16%)	18 (36%)
No	42 (84%)	32 (64%)
P value	0.03 (Fisher test)	

- As mentioned in table 1, in Group A total of 50 Premature Neonates in whom Oral Propranolol was given, ROP was diagnosed in 8 (16%) Premature Neonates and not diagnosed in 42 (84%) Premature Neonates.
- While the Group B consisted of total of 50 Premature Neonates in whom 5% Dextrose was given as placebo, ROP was diagnosed in 18 (36%) Premature Neonates and not diagnosed 32 (64%) Premature Neonates.
- Progression of ROP was 16% less significant in Group A in whom Oral Propranolol was given prophylactically in comparison to Premature Neonates in whom Oral Propranolol was not given i.e., Group B is (36%).

ROP among Neonates

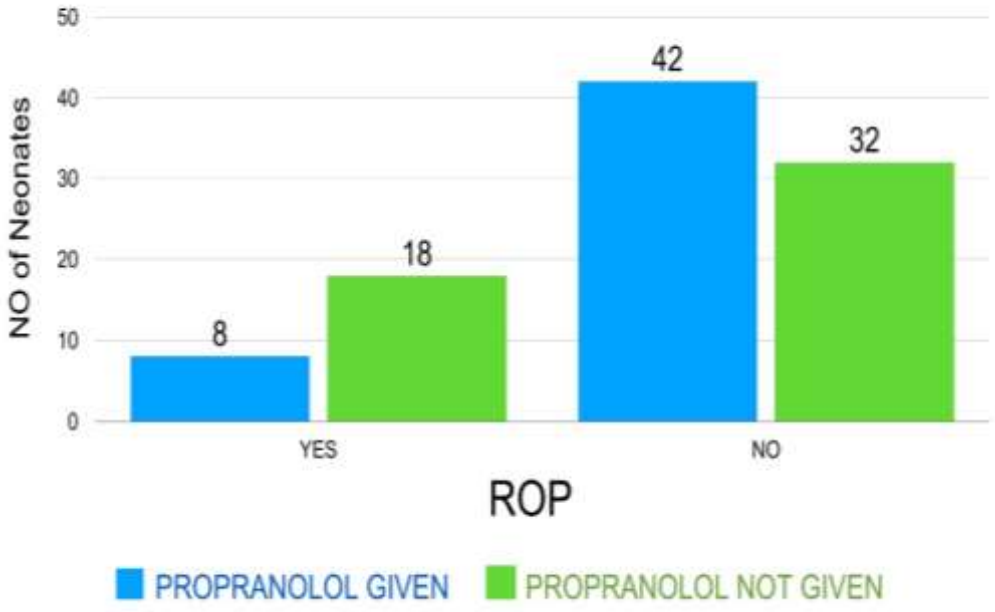

Figure 1: ROP Result

Table 2: Intervention Given

Intervention	**Group A Oral Propranolol Given**	**Group B Placebo Group**	**P value (Fischer test)**
Pan Retinol Photocoagulation (PRP) Laser	6 (12%)	15 (30%)	0.04
PRP with Anti-VEGF	0	3 (6%)	0.24
No Intervention	44 (88%)	32 (64%)	0.009

- As mentioned in the table 2, majority of Premature Neonates in Oral Propranolol group (Group A) required no intervention (88 %), as compared to those without Oral Propranolol therapy (64%) (Group B).

- PRP laser was required (36%) more in Premature Neonates without propranolol therapy (Group B).
- The use of Anti-VEGF was reported in 6% Premature Neonates in Non-Propranolol Group (Group B).

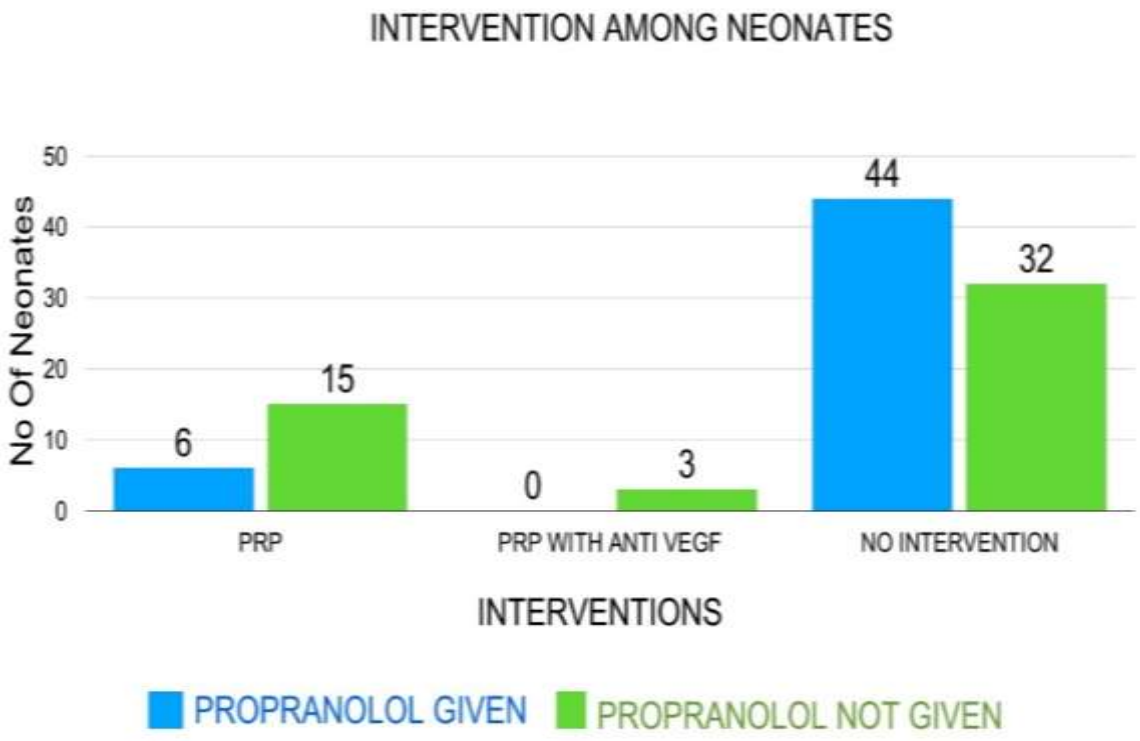

Figure 2: Intervention Given

- In above figure 2. Premature Neonates who were selected in the present observational study and divided into Group A in whom Oral Propranolol was given and Group B Placebo Group, which were further studied to look for the type of intervention required.
- There were 3 groups of treatment made as follows: PRP Laser, Anti VEGF therapy and no intervention. PRP Laser was required as treatment in 6% and 15% of Group A in whom Oral Propranolol was given and Group B Placebo Group respectively.
- While 3% Premature Neonates required Anti-VEGF treatment in whom we did not give Oral Propranolol and the Premature Neonates given Oral Propranolol did not require Anti-VGEF therapy.
- The Premature Neonates in whom Oral Propranolol was given no intervention was required in 44% Premature Neonates and similarly no intervention was required for 32% Premature Neonates who received placebo.
- Propranolol is simple, inexpensive, well tolerated and with nearly no side effects.[4]

- The bi-center trial carried out in Haifa and Jerusalem, Israel in Makhoul IR and Peleg O et al studies shows the result 2 of the 10 (20%) premature infants randomized to Propranolol Group and 4 out of 10 (40%) Placebo group required Intervention for ROP. Laser treatment was carried out in 4 out of 19 (21%) Preterm in Oral Propranolol group and 8 of 19 (42%) Preterm of Placebo Group.
- The bicenter trial carried out in the study of Filippi L, Cavallaro G et al at Firenze and Milano, Italy 10 of 26 (4%) controls and four of 25 (16%) preterm under treatment for ROP. With CI of 95% the relative risk is 0.42. Preterm Neonates requiring laser treatment in Oral Propranolol group is 8 of 50 (16%) and 19 of 52 (36%) in control group.
- Thus, in both the above studies the use of Oral Propranolol is promising in contrast to the other available treatment options like Laser therapy wherein myopia and peripheral visual outcome is poor, while the Anti-VEGF injectable has increase chance of reoccurrence and retinal detachment. [7]
- In mice studies it has been observed that Oral Propranolol downregulates retinal levels of angiogenic factors such as VEGF and decrease the hypoxia induced retinal neovascularisation.[3]
- Hence, the use of Oral Propranolol is promising in the treatment of ROP in Premature infants in whom oxygen supplementation has been used unregulated.
- Propranolol helps in the prevention of ROP and with the treatment in Premature infants diagnosed with ROP.
- Early intervention with Oral Propranolol in Premature Neonates has shown promising result of decreasing the incidence of ROP with decreasing the need for further therapy with laser or Anti-VEGF factor.

CONCLUSION

The present study concludes that, in Group A in which Oral Propranolol was given incidence of progression of ROP was 16% while 36% in Group B in whom Oral Propranolol was not given. The usefulness of Oral Propranolol in the management of ROP was highlighted in the study. As ROP is dependable on non oxygen requiring parameters like gestational age and birth weight, due to the increasing incidence of low birth weight and Premature Neonates there is a rising trend in the ROP. Hence early therapy with Oral Propranolol has resulted in the decreasing in the progression of the disease to next stage and, thus the study recommends that the management of ROP requires use of Oral Propranolol. Hypotension, Bradycardia and Hypoglycemia are the common side effects of propranolol, but were not observed in our conducted study.

ABBREVIATION

ROP: Retinopathy of Prematurity.

ELBW: Extremely low birth weight.

HIF-1: Hypoxia Inducible Growth Factor.

VEGF: Vascular Endothelial Growth Factor.

IGF-1: Insulin like Growth Factor 1.

Epo: Erythropoietin.

PlGF: Placental Growth Factor.

NO: Nitric Oxide.

B-Ars: Beta-Adrenoreceptors.

USA: United State of America.

GA: Gestational Age.

NICU: Neonatal Intensive Care Unit.

AV: Atrio-Ventricular.

AKI: Acute Kidney Injury.

IVH: Intraventricular Hemorrhage.

PRP: Pan-Retinal Photocoagulation.

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