Open Access

Original Article

# Efficacy of Oral Propranolol in Prevention of Severe Retinopathy of Prematurity: A Randomized Clinical Trial Study

## Pourang Mohammadi[1], Homa Babaei[2,*], Hadi Mohsenpour[2], Pejvak Azadi[3]

1. School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran
2. Department of Pediatrics, School of Medicine, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
3. Department of Ophthalmology, School of Medicine, Imam Khomeini Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran

## ABSTRACT

**Background:** Retinopathy of prematurity (ROP) is a disease of the retinal vessels in premature newborns and can lead to a wide range of vision disorders from minor correctable visual acuity defects to retinal detachment. The present study aimed to determine the efficacy of oral propranolol in the prevention of severe ROP.

**Methods:** This randomized clinical trial study was conducted on 50 preterm newborns with retinopathy stage I or II without plus disease hospitalized at Imam Reza Hospital of Kermanshah city, Kermanshah, Iran. The samples were randomized into two groups (n=25 each). The intervention group received 0.5 mg/kg propranolol orally every 8 hours and was continued until retinal vascularization completion or the need for treatment by laser therapy or Avastin injection. In contrast, the control group received only routine care without receiving propranolol. Afterward, the two groups were compared in terms of progression to stage III and above of retinopathy, plus disease, retinal detachment, need for laser therapy or Avastin injection, and the duration of the retinal vascularization completion. Adverse events related to propranolol, such as hypoglycemia, hypotension, and bradycardia, were continuously monitored during the study. Finally, the data were entered into SPSS24 software and analyzed.

**Results:** The two groups did not differ significantly in terms of demographic variables at the beginning of the study. The means of gestational age and numbers (%) of boys were 29±1.29 vs. 29.20±1.35 and 14 (56%) vs. 11 (44%) in the intervention and control groups, respectively. After the intervention, the duration of the completion of retinal vessels (day) was shorter in newborns receiving oral propranolol (61.04±6.13) than in the control group (70.08±5.72) (P<0.001). Moreover, the recovery rate from retinopathy and the incidence rate of plus disease were 88% vs. 68% and 4% vs. 12% in the intervention and control groups, respectively; however, this difference was not statistically significant (P>0.05). No adverse events related to propranolol were observed.

**Conclusion:** Although the duration of the completion of retinal vascularization was shorter in newborns receiving oral propranolol, it was not effective in preventing severe ROP. Multicenter clinical trial studies with a higher sample size are recommended.

**Keywords:** Efficacy, Oral propranolol, Retinopathy of prematurity

## Introduction

Retinopathy of prematurity (ROP), which was known in the past as "retrolental fibroplasia", is a disease that may occur in the retina of some premature newborns (1). This disease occurs due to a delay in the normal vascularization of the retina, followed by the proliferation of abnormal vessels into the vitreous, which can lead to a wide range of visual impairments, from partially correctable defects to complete detachment of the retina and blindness (2, 3). In the last decade, blindness related to ROP has increased, especially in developing countries, despite the advancement in neonatal care methods. ROP is becoming the most common cause of childhood blindness in developing countries (4). The prevalence of ROP varies in different regions of Iran. A recent meta-analysis study reported its prevalence to be 23.5% (5). Another meta-analysis study in Iran reported

* *Corresponding author*: Homa Babaei, Department of Pediatrics, School of Medicine, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran. Tel: +983834276305; Email: Homa_babae@yahoo.com

an increase in the prevalence of ROP from 6% in 2001 to 24.1% in 2016 (6).

The most important risk factors of this disease include premature birth, especially before the 31st week of pregnancy, and birth weight of less than 1,500 g. Other causes are mentioned as apnea, intraventricular hemorrhage, respiratory disorders, vitamin E deficiency, heart disease, increased blood carbon dioxide, increased oxygen consumption, acidosis, hypoxemia, bradycardia, and receiving blood (7-9).

Retinopathy of prematurity is mostly asymptomatic, thus newborns at risk should be screened. Based on the national guidelines, the recommended screening for ROP should be performed for all preterm newborns with a gestational age of ≤ 34 weeks or birth weight of ≤ 2,000 g on the 28th day of birth (10).

However, ROP is still the most common preventable cause of vision impairment in childhood. Considering the progressive course of the ROP, treatment measures in the early stages are much more effective because, in the final stages of the disease, the treatment is highly difficult, expensive, and in some cases impossible (11). In stages I and II of retinopathy, newborns are usually only followed up; nevertheless, from stage III onwards, treatment with laser or intravitreal injection of anti-vascular endothelium growth factor drugs, such as Avastin, begins. However, due to the need for anesthesia interventions, side effects (e.g., bleeding), corneal opacity in laser treatment, and problems related to Avastin injection (e.g., the painfulness of the treatment process and the possibility of endophthalmitis) attention has been directed to less invasive interventions, such as oral propranolol (12, 13). Propranolol blocks beta-2 adrenoreceptors. The effect of oral propranolol in preventing angiogenesis has been proven in animal models (14).

Generally, in the pathogenesis of ROP, there are two completely different phases, including the first phase, vascularization, and the second phase, neovascularization. Our knowledge and understanding of this pathogenic process will help us to clarify our ideas about disease. Hence, the discovery of the pathophysiology of ROP has increased the use of selective therapies that target the angiogenesis pathway (15, 16). Some studies have suggested that the beta-adrenergic system may be involved in the development of ROP. For example, the polymorphism of beta-adrenergic receptors has been introduced as the main reason for the lower incidence of retinopathy in many

black infants compared to non-black ones (17). Animal studies have also demonstrated the effect of β2-adrenergic (β2-AR) on improving ROP (18). The results of these studies have mentioned that blocking β2-AR can reduce hypoxia-induced vascularization. (19). On the other hand, considering that blocking beta-adrenergic receptors causes the destruction of infantile hemangiomas that have abnormal angiogenesis, propranolol (nonselective beta-blocker) may also prevent the development of retinopathy with such a similar mechanism (20). In 2008, French researchers evaluated the efficacy of propranolol on the regression of infantile hemangioma for the first time (21). Common side effects of propranolol include hypotension, hypoglycemia, and bradycardia, which are usually transient.

The first study that showed the effect of propranolol on the prevention and treatment of ROP was performed in 2010 (22). Since then, several studies have been conducted in different countries about the efficacy of propranolol on ROP. The results of some studies have shown that propranolol reduces neovascularization and prevents the progression of ROP stage II to more advanced stages (stage III and above) (23-25). In a clinical trial conducted by Ozturk et al. with the aim of investigating the effect of oral propranolol in the treatment of ROP, 126 newborns with stages 0 to II retinopathy were randomly divided into control and treatment groups with propranolol at a dose of 2 mg/kg/day. The results of the study showed that newborns with stage II retinopathy benefited more from propranolol treatment compared to infants with stage 0 or I retinopathy (26). However, the studies conducted in this field are limited and their results regarding the efficacy of propranolol are contradictory. Therefore, the present study was designed and implemented to investigate the efficacy of oral propranolol in the prevention of severe ROP.

## Methods

This randomized clinical trial study (RCT) was designed and implemented with the aim of investigating the efficacy of oral propranolol in the prevention of severe retinopathy in preterm newborns admitted to the neonatal intensive care unit of Imam Reza Hospital of Kermanshah, Iran. The study was carried out over 12 months, from Sep 2021 to Aug 2022. In this study, the selection of samples was based on available sampling. Randomization of newborns was conducted by the computer and statistic consultant using a random number generator

system. Considering a 95% confidence interval and 90% power, the minimum required sample size was determined at 25 newborns in each group. All preterm newborns with a gestational age of ≤ 34 weeks or birth weight of ≤ 2,000 g underwent ophthalmological examination on the 28th day of birth. Among them, newborns with stage I or II ROP without plus disease being hospitalized for at least 1 week after starting the study were enrolled in the study. On the other hand, newborns with major congenital malformation, cardiovascular disease, recurrent bradycardia, ocular anomalies, ROP stage III and above, renal failure, and grade 2 and 3 intraventricular hemorrhage, as well as newborns who needed oxygen therapy for more than 28 days postnatal, were excluded from the study.

All ophthalmological examinations were performed by an experienced retina subspecialist. The retina subspecialist responsible for the eye examination and a nurse responsible for collecting patients' data were unaware of the assignment of infants into groups (the study was double-blind). Eligible newborns were randomly divided into intervention and control groups (n=25 each).

Routine care included feeding support, cardiorespiratory monitoring, daily blood pressure monitoring, and periodic eye examination. The intervention group received routine treatment in addition to 0.5 mg/kg propranolol (Hakim Co, Thran, Iran) orally every 8 hours, and its administration was continued until retinal vascularization completion on ophthalmic examination or the need for treatment by laser therapy or intraocular Avastin administration.

In contrast, the control group underwent only routine care that was given to preterm newborns and they did not receive propranolol. Considering that in addition to investigating the efficacy of propranolol, we also wanted to check the safety of the drug in preterm newborns with retinopathy, it was necessary for the newborns to be hospitalized and under monitoring for at least 1 week after the start of the treatment. Newborns in both groups were monitored for bradycardia, apnea, and hypotension for at least 1 week after entering the study, and the medication was discontinued in case of any side effects. After the discharge of the newborn, the occurrence of any problem, such as lethargy and poor feeding, was followed up through phone calls.

Furthermore, the newborns of both groups were examined by a retinal subspecialist every 1 to 2 weeks until retinal vascularization completion. Finally, the two groups were compared in terms of progression to stage III and above of retinopathy, plus disease, retinal detachment, need for laser therapy or Avastin injection, and the duration of follow-up days until the retinal vascularization completion.

For all newborns, all independent variables, including demographic, and clinical variables, such as postnatal age, gender, gestational age, birth weight, duration of receiving $O_2$, history of blood transfusion, history of receiving surfactant, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), and the stage of retinopathy before the intervention, as well as all data related to dependent variables, including bradycardia, apnea, hypotension, progression to stage III and above of retinopathy, plus disease, retinal detachment, the need for laser therapy or Avastin injection, and the duration of follow-up days until the retinal vascularization completion, were entered into the pre-designed form.

Before data collection, the aims of the research were explained to the parents, then informed consent was obtained from them. This study was approved by the Deputy of Research and Ethics Committee of Kermanshah University of Medical Sciences (ID: IR.KUMS.REC.1400.258). This study was also approved by the Iranian Registry of Clinical Trials (ID:IRCT20101018004961N12).

### Statistical Analysis

Data were analyzed using SPSS24. Mean, standard deviation (SD), and frequency (%) were used for descriptive analyses. Then, an independent sample t-test was used to compare the mean of quantitative variables in two groups, and the Chi-square test or Fisher's exact test to check the relationship between qualitative variables. The significance level was considered less than 0.05.

## Results

A total of 58 preterm newborns with retinopathy stage I or II entered the study. Five newborns declined to participate. One newborn was excluded from the intervention group and two cases from the control group due to discharge with parental consent before completing the study (the attrition rates were 7.4 and 3.8 in intervention and control groups, respectively). Finally, 50 preterm newborns, who had the eligibility criteria, were enrolled and participated in two groups of intervention (n=25) and control

(n=25). Figure 1 details the flow of participants in the trial. Table 1 shows the baseline and clinical

characteristics of the newborns in the intervention and control groups. The means of
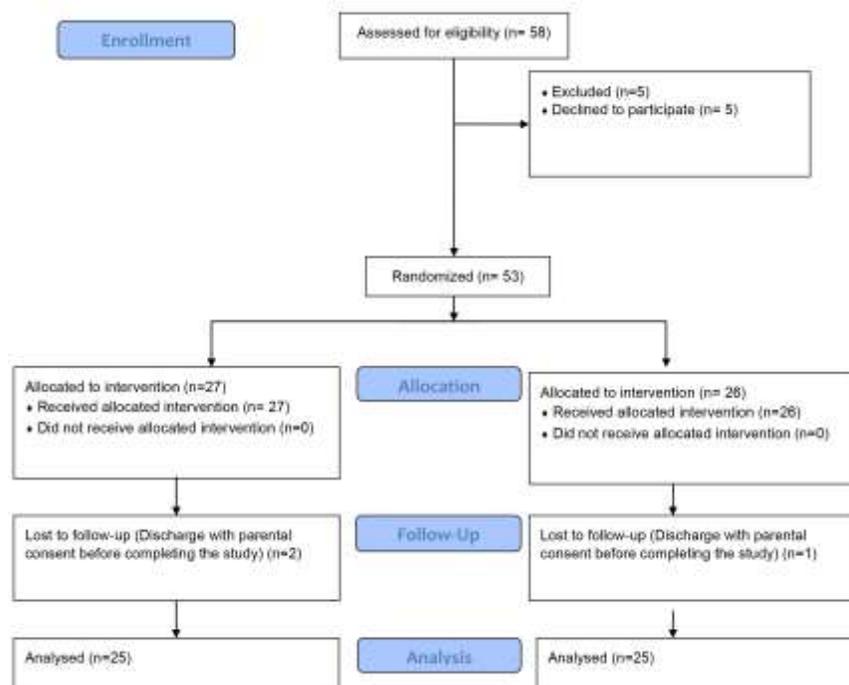


**Figure. 1.** Flow chart of study on oral propranolol and severe retinopathy of prematurity

**Table 1.** Comparison of baseline and clinical variables in the intervention and control groups

| Qualitative Variables | | Intervention group n (%) | Control group n (%) | P-Value* |
|---|---|---|---|---|
| Gender | Girl | 11 (44) | 14 (56) | |
| | Boy | 14 (56) | 11 (44) | 0.396 |
| | Total | 25 (100) | 25 (100) | |
| History of blood transfusion | Yes | 11 (44) | 7 (28) | |
| | No | 14 (56) | 18 (72) | 0.239 |
| | Total | 25 (100) | 25 (100) | |
| History of receiving surfactant | Yes | 20 (80) | 21 (84) | |
| | No | 5 (20) | 4 (16) | 0.713 |
| | Total | 25 (100) | 25 (100) | |
| Intraventricular hemorrhage (grade 1) | Yes | 6 (24) | 4 (16) | |
| | No | 19 (76) | 21 (84) | 0.480 |
| | Total | 25 (100) | 25 (100) | |
| Necrotizing enterocolitis | Yes | 2 (8) | 3 (12) | |
| | No | 23 (92) | 22 (88) | 0.637 |
| | Total | 25 (100) | 25 (100) | |
| Patent ductus arteriosus | Yes | 7 (28) | 3 (12) | |
| | No | 18 (72) | 22 (88) | 0.157 |
| | Total | 25 (100) | 25 (100) | |
| Stage of retinopathy before intervention | Stage 1 | 12 (48) | 11 (44) | |
| | Stage 2 | 13 (52) | 14 (56) | 0.777 |
| | Total | 25 (100) | 25 (100) | |
| **Quantitative variable** | **Number** | **Mean** | **SD** | **P-Value**** |
| Postnatal age at first eye examination (day) | 25 | 29.32 | 1.18 | |
| | 25 | 28.88 | 1.09 | 0.165 |
| Gestational age (week) | 25 | 29.00 | 1.29 | |
| | 25 | 29.20 | 1.35 | 0.595 |
| Birth weight (g) | 25 | 1168 | 1167.6 | |
| | 25 | 122.64 | 119.45 | 0.991 |
| Duration of receiving $O_2$ (day) | 25 | 4.87 | 4.96 | |
| | 25 | 2.15 | 1.37 | 0.815 |

*Chi square test      **Independent sample t-test

postnatal age of newborns at the time of diagnosing ROP at the first ophthalmic examination were 29.32±1.18 and 28.88±1.09 days in the intervention and control groups, respectively. In terms of the stage of retinopathy before the intervention, 52% and 56% of the subjects were in stage II in the intervention and control groups, respectively. The two groups had no statistically significant differences in terms of gender, postnatal age, gestational age, birth weight, history of blood transfusion, history of receiving surfactant, duration of receiving oxygen, IVH (grade 1), NEC, PDA, and retinopathy stage at the beginning of the study, which showed that the randomization was done properly (Table 1).

Table 2 presents the primary and secondary outcomes after the intervention. As can be seen, the results of the independent sample t-test showed that the duration of the retinal vascularization completion in the intervention group (61.04±6.13) happened 10 days earlier than in the control group (70.08±5.72), and this difference was statistically significant (P<0.001). Based on the result of the Chi-square test, the recovery rate from retinopathy was 88% in the intervention group, while it was 68% in the control group; however, this difference was not statistically significant (P=0.088). Moreover, the incidence rate of plus disease was lower in the intervention group than in the control group (4% vs. 12%); however, this difference was not statistically significant (P=0.297).

**Table 2.** Comparison of the primary and secondary outcomes in two intervention and control groups

| Qualitative Variables | | Intervention group Number (%) | Control group Number (%) | P-Value |
|---|---|---|---|---|
| Stage of retinopathy after intervention | Recovery | 22 (88) | 17 (68) | 0.088* |
| | Stage III | 3 (12) | 8 (32) | |
| | Total | 25 (100) | 25 (100) | |
| Plus disease and stage III | Yes | 1 (4) | 3 (12) | 0.297** |
| | No | 24 (96) | 22 (88) | |
| | Total | 25 (100) | 25 (100) | |
| **Quantitative variable** | **Number** | **Mean** | **S.D** | **P-Value** |
| The duration of the retinal vascularization completion after intervention(day) | 25 | 61.04 | 6.13 | 0.001***< |
| | 25 | 70.08 | 5.72 | |

*: Chi square test     **: Fisher's exact test     ***: Independent sample t-test

It should be noted that all the newborns studied had retinopathy in zone 2 and we did not have any cases in zone 1 or 3. No cases of stage 4 or 5 retinopathy were reported in the studied newborns.

All newborns who needed treatment, including 3 neonates in the intervention group and 8 in the control group, were treated with intraocular Avastin injection, and none of the newborns received laser treatment. Any side effects caused by the use of oral propranolol, such as apnea, hypoglycemia, and hypotension, did not occur in any of the studied newborns.

## Discussion

As preterm births have become more common in recent years, so have the diseases associated with them. One of the most important of these diseases is ROP (18). Therefore, in this study, we were looking for a less invasive method with fewer side effects to treat this disease, which is the most common cause of preventable visual impairment in newborns.

The results of our RCTs showed that the duration of the completion of retinal vessels was shorter in newborns receiving oral propranolol (61.04±6.13) than in the control group (70.08±5.72) (P<0.001). Additionally, the recovery rate from retinopathy and the incidence rate of plus disease were 88% vs. 68% and 4% vs. 12% in the intervention and control groups, respectively; however, this difference was not statistically significant (P>0.05). Although this was not statistically significant, considering that 3 out of 25 newborns in the intervention group had stage III retinopathy compared to 8 out of 25 newborns in the control group, it showed that it was clinically significant. The non-significance of the p-value seemed to be due to the small sample size.

In line with the results of the study, in a study conducted by Filippi et al. to determine the safety and efficacy of oral propranolol in preterm newborns with an early phase of retinopathy, the newborns who received oral propranolol 0.5 mg/kg/6 hours, the incidence of stage III retinopathy or stage III with plus disease was 52% and 42% less than the control group, respectively. The need for laser therapy and treatment with

intravitreal bevacizumab was 52% less than in the control group. However, side effects, especially hypotension, bradycardia, and sepsis, were reported in 19.2% of these newborns treated with propranolol (24). In a study conducted by Makhoul et al. on 20 premature newborns with ROP (stage I or II) with a gestational age of 24 to 28 weeks and a birth weight of less than 1,500 g, the need for aggressive treatments, such as laser in newborns receiving propranolol, was less than that in the placebo group; however, due to the small sample size, it was not statistically significant (25). In addition, in a meta-analysis study conducted by Stritzk et al. to evaluate oral propranolol in the prevention of ROP, 6 studies with 461 newborns were included in the analysis. Finally, the evaluation of this review showed that oral propranolol had a significant and effective effect in preventing severe ROP in premature newborns of ≤ 32 weeks of gestational age. In the studies examined in this review, the progression of the disease to stage II or higher, the incidence rate of plus disease, and the need for treatment for laser or anti-vascular endothelial growth factors injection were significantly reduced in newborns receiving oral propranolol (15). The results of a study by Ozturk et al. on 126 very preterm newborns reported that propranolol had no effect on the improvement of ROP in stages 0 and I; however, it could be effective in the treatment of ROP stage II. The researchers of this study stated that the reason for the different efficacy of propranolol in different stages of ROP was due to the fact that retinal tissue was more hypoxic in stage II; therefore, the efficacy of beta-blockers was greater for these tissues (26). In a study by Mirjalili et al., although the rate of improvement of ROP in the propranolol group was higher than in the control group (81.34% vs. 66.77%), this difference was not statistically significant (27), this finding was consistent with the recovery rate in our study.

Plus disease is the most important pathology in ROP monitoring. The presence of this disease indicates that ROP is progressive. It is one of the most important criteria in clinical and treatment decisions for ROP. In our study, the incidence rate of plus disease in the intervention group was lower than in the control group (4% vs. 12%); however, this difference was not statistically significant. In the study by Ozturk et al., the same results were obtained; in other words, the incidence rate of the plus disease in the propranolol intervention group was lower than that in the placebo group; however, it was not

statistically significant (25).

The present study had several strengths and limitations. The most important limitation of this single-center study was the small sample size of premature newborns participating in the study. However, the long-term follow-up of newborns in terms of vision for at least 75 days after the intervention and the safety evaluation of oral propranolol in addition to its efficacy in the treatment of retinopathy were the strengths of this study.

## Conclusion

The results of our study showed that propranolol with a dose of 1.5 mg/kg/day cannot prevent the progression of retinopathy to stages III and above; nonetheless, it was able to shorten the duration of retinal vessel completion. Multicenter clinical trial studies with a higher sample size are recommended.

## Acknowledgments

## Conflicts of interest

The authors declare that there is no conflict of interest.

## References

1. Yau GS, Lee JW, Tam VT, Liu CC, Yip S, Cheng E, et al. Incidence and risk factors of retinopathy of prematurity from 2 neonatal intensive care units in a Hong Kong Chinese population. The Asia-Pacific Journal of Ophthalmology. 2016;5(3):185-91.
2. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Chan RP, Berrocal A, et al. International classification of retinopathy of prematurity. Ophthalmology. 2021;128(10):e51-e68.
3. Hamad AE, Moinuddin O, Blair MP, Schechet SA, Shapiro MJ, Quiram PA, et al. Late-onset retinal findings and complications in untreated retinopathy of prematurity. Ophthalmology Retina. 2020;4(6):602-12.
4. Wang L, Zhang Z, Tao M, Li M, Wang Y. The prevalence of retinopathy of prematurity in the mainland of China from 2008 to 2018. [Zhonghua yan ke za Zhi] Chinese Journal of Ophthalmology. 2021;57(5):379-85.
5. Azami M, Jaafari Z, Rahmati S, Farahani AD, Badfar G. Prevalence and risk factors of retinopathy of prematurity in Iran: a systematic review and meta-analysis. BMC ophthalmology. 2018;18(1):1-14.
6. Maroufizadeh S, Almasi-Hashiani A, Samani RO, Sepidarkish M. Prevalence of retinopathy of

prematurity in Iran: a systematic review and Meta-analysis. International Journal of Ophthalmology. 2017;10(8):1273.

7.  Edy Siswanto J, Sauer PJ. Retinopathy of prematurity in Indonesia: Incidence and risk factors. J Neonatal Perinatal Med. 2017;10(1):85-90.

8.  Akkawi MT, Shehadeh MM, Shams ANA, Al-Hardan DM, Omar LJ, Almahmoud OH, et al. Incidence and risk factors of retinopathy of prematurity in three neonatal intensive care units in Palestine. BMC ophthalmology. 2019;19(1):1-7.

9.  Leng Y, Huang W, Ren G, Cai C, Tan Q, Liang Y, et al. The treatment and risk factors of retinopathy of prematurity in neonatal intensive care units. BMC ophthalmology. 2018;18(1):1-8.

10. Roohipoor R,Karkhaneh R,Farahani A, *et al.*Retinopathy of prematurity screening criteria in iran:new screening guidelines. Archives of Disease in Childhood-Fetal and Neonatal Edition .2016;101:F288-F293.

11. Wadhwani M, Vashist P, Singh SS, Gupta V, Gupta N, Saxena R. Prevalence and causes of childhood blindness in India: A systematic review. Indian journal of ophthalmology. 2020;68(2):311.

12. Mueller B, Salchow DJ, Waffenschmidt E, Joussen AM, Schmalisch G, Czernik C, Bührer C, Schunk KU, Girschick HJ, Winterhalter S. Treatment of type I ROP with intravitreal bevacizumab or laser photocoagulation according to retinal zone. Br J Ophthalmol. 2017 Mar;101(3):365-370.

13. Geloneck MM, Chuang AZ, Clark WL, Hunt MG, Norman AA, Packwood EA, Tawansy KA, Mintz-Hittner HA; BEAT-ROP Cooperative Group. Refractive outcomes following bevacizumab monotherapy compared with conventional laser treatment: a randomized clinical trial. JAMA Ophthalmol. 2014 Nov;132(11):1327-33.

14. Lavine JA, Sang Y, Wang S, Ip MS, Sheibani N. Attenuationof choroidal neovascularization by β(2)-adrenoreceptor antagonism. JAMA Ophthalmol. 2013;131(3):376-382
    doi:10.1001/jamaophthalmol.2013.1476

15. Stritzke A, Kabra N, Kaur S, Robertson H, Lodha A. Oral propranolol in prevention of severe retinopathy of prematurity: a systematic review and meta-analysis. Journal of Perinatology. 2019;39(12):1584-94.

16. Chan-Ling T, Gole GA, Quinn GE, Adamson SJ, Darlow BA. Pathophysiology, screening and treatment of ROP: a multi-disciplinary perspective. Progress in retinal and eye research. 2018;62:77-119.

17. Group ETfRoPC. The incidence and course of retinopathy of prematurity: findings from the early

18. treatment for retinopathy of prematurity study. Pediatrics. 2005;116(1):15-23.

18. Fierson W. American Academy of Pediatrics section on ophthalmology; American Academy of ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131(1):189-95.

19. 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 β-adrenoreceptor blockade. Investigative ophthalmology & visual science. 2011;52(1):155-70.

20. Baker JG. The selectivity of β-adrenoceptor antagonists at the human β1, β2 and β3 adrenoceptors. British journal of pharmacology. 2005;144(3):317-22.

21. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taieb A. Propranolol for severe hemangiomas of infancy. N Engl J Med. (2008) 358:2649–51. doi: 10.1056/NEJMc0708819

22. 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. doi: 10.1186/1471-2431-10-83

23. Rathi S, Jalali S, Patnaik S, Shahulhameed S, Musada GR, Balakrishnan D, et al. Abnormal complement activation and inflammation in the pathogenesis of retinopathy of prematurity. Frontiers in immunology. 2017;8:1868.

24. Filippi L, Cavallaro G, Bagnoli P, Dal Monte M, Fiorini P, Donzelli G, et al. Oral propranolol for retinopathy of prematurity: risks, safety concerns, and perspectives. The Journal of pediatrics. 2013;163(6):1570-7. e6.

25. Makhoul IR, Peleg O, Miller B, Bar-Oz B, Kochavi O, Mechoulam H, et al. Oral propranolol versus placebo for retinopathy of prematurity: a pilot, randomised, double-blind prospective study. Archives of disease in childhood. 2013;98(7):565-7.

26. Ozturk MA, Korkmaz L. The efficacy of propranolol in very preterm infants at the risk of retinopathy of prematurity: Which newborn and when? Int Ophthalmol. 2019 Sep;39(9):1921-1930.

27. Mirjalili A, Manaviat MR, Noori-Shadkam M. Evaluation of the oral propranolol effect on retinopathy of prematurity: randomized clinical trial. World Journal of Peri and Neonatology. 2019;2(1):37-43.