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ORIGINAL PAPER

The efficacy of propranolol in very preterm infants at the risk of retinopathy of prematurity: Which newborn and when?

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Abstract
Purpose Retinopathy of prematurity (ROP), a proliferative vitreoretinopathy resulting from the vascular disorder of the retina, is the most frequent cause of blindness in childhood. In our time, ROP in advanced stage, a serious problem in premature infants, has no other treatment more effective and with fewer side effects than laser photocoagulation (LPC) treatment, which narrows visual field. The search for methods with fewer side effects than LPC has increased in recent times for the treatment of ROP. We aimed to investigate the effects in question of propranolol on ROP in various stages (stages 1, 2, and 3 ROP).
Methods This study is designed as a randomized, placebo-controlled, single-centered, double-blind clinical trial with parallel groups. A total of 126 very preterm infants, followed up in our unit from April 2011 to January 2013, were randomly selected and included in our study. They were separated into the groups of 0, 1, and 2 depending on their stage of ROP. In addition, all the patients were divided into control group (CG) and propranolol treatment group (PTG). While the cases in the CG were administered physiological saline solution, the cases in the PTG were administered propranolol (2 mg/kg/day) in the neovascularization phase (second phase) of the ROP.
Results Propranolol given to the group of stage 0–1 ROP was observed to have had no effect on the level of statistical significance between the CG and PTG in terms of increase in ROP stages ($p > 0.05$). However, propranolol was found to be more useful in patients with stage 2 ROP ($p < 0.05$).
Conclusion When given in the neovascularization phase of the ROP, propranolol 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.

Keywords Very preterm infant · Propranolol · Retinopathy of prematurity · Efficacy

Introduction

Retinopathy of prematurity (ROP), which is a disease of retinal vascular development in preterm infants, is one of the leading causes of blindness in childhood worldwide. The incidence of the disease is closely related to gestational age and birth weight [1].

The studies conducted on animals with a view to understanding the disease have enabled us to obtain a considerable amount of important data [2, 3]. In the pathogenesis of the disease, in particular, the stages develop diametrically opposite to each other (the first

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phase, vasoobliteration, and the second phase, neovascularization) which helped us to form our ideas on the disease. This concept of biphasic phase (i.e., biphasic theory) has been quite useful in understanding the pathophysiology of ROP, which is rather complicated. In addition, the appearance of data demonstrating the importance of vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) in these phases and the effects of the β_2-adrenergic (β_2-AR) system on ROP have helped mature the thoughts about ROP treatment [4–7].

The current therapy for ROP in the advanced stage, in spite of it being destructive in terms of the consequences it gives rise to, is laser photocoagulation (LPC) therapy; as is known, this treatment modality has side effects causing loss of visual field [8]. Therefore, both ophthalmologists and pediatrists have begun to search treatment modalities with fewer side effects. Such search has turned attention to propranolol, which is used in hemangioma treatment [7, 9]. We also planned to study in order to understand the possible effects of propranolol on ROP in its neovascularization phase.

Methods

A double-blind, randomized, controlled study was conducted with 147 newborns who were under the ROP risk. Very preterm infants who were admitted to our hospital from August 2011 to January 2013 with a gestational age below 32 weeks, a birth weight below 1500 g, and with stages 0–1, and 2 ROP were included in the study. Twenty-one patients who were initially taken to study were excluded due to various reasons. As a result, we completed our study with 126 very preterm infants. The data regarding all the patients were transferred to the forms prepared throughout their follow-up, and the records were preserved.

Those cases meeting the gestational weight and age criteria mentioned earlier were selected and randomly divided according to their stage of ROP. Control (CG) and propranolol treatment group (PTG) were arranged in each ROP group. While the PTG received propranolol treatment in the second phase of the disease (this phase is the neovascularization phase and is also known as the essential phase), the CG received saline solution only in the same period (Tables 1, 2, 3 and 4 and Fig. 1).

Propranolol (2 mg/kg/day) was given to the all PTG cases (stages 0, 1 and 2) by mouth 30 min. before feeding. It was dissolved in physiological saline solution. No leftover solution given orally was used again, i.e., we prepared fresh solutions on each occasion. Oral propranolol treatment and retinal examination were continued until retinal vascularization was completed in both groups.

It is suggested that postmenstrual age be considered while monitoring ROP and determining its phases [1]. In addition, it is known that the second phase of ROP starts at 32nd postmenstrual week and the earlier periods are consistent with the first-phase period of ROP [5, 10].

Care was taken to ensure that the treatment session was at the end of phase 1 and at the beginning of phase 2, i.e., in the period between the end of vasoobliteration (phase 1) and the beginning of neovascularization (phase 2) [1]. Postmenstrual age was considered in the timing of propranolol therapy. We used the period over the 32nd postmenstrual age as the base for the second phase of ROP. The patients were evaluated concomitantly by two separate ophthalmologists blind as to which patient had received propranolol.

For ROP scoring, an international scoring system (International Classification of Retinopathy of Prematurity—ICROP) was used [11]. The retina was divided into three zones (I, II, III) [1]. Stage 0: no ROP sign in the retina, stage 1: the sighting of a thin whitish demarcation line between the avascular and vascular retinal regions, and stage 2: the appearance of a ridge characterized by the height, width, and volumetric gain of the demarcation line. While stage 3 was defined as the appearance of irregularities and revascularization inside the ridge, plus disease was defined as the increase in tortuosity and dilatation [1].

Early treatment strategy was applied for LPC treatment. Treatment decisions almost always were based on the presence or absence of plus disease. Any stage of ROP with plus disease in zone I or stage 3 ROP without plus disease in zone I or stage 2 or 3 ROP with plus disease in zone II was considered sufficient for LPC [12, 13].

An international scoring system was used in scoring bronchopulmonary dysplasia (BPD) [14]. Premature rupture of membranes (PROM) was considered positive when it occurred more than 18 h after the

Table 1 Demographic distribution of study groups, their distribution, accompanying diseases, and their significance

Conditions associated with ROP	Groups of stage 0 ROP (*n*:48)		Groups of stage 1 ROP (*n*:40)		Groups of stage 2 ROP (*n*:38)	
	CG (*n*:29) (%) median ± SD	PTG (*n*:19) (%) median ± SD	CG (*n*:21) (%) median ± SD	PTG (*n*:19) (%) median ± SD	CG (*n*:18) (%) median ± SD	PTG (*n*:20) (%) median ± SD
Female/male	18/11	10/9	7 /14	7/12	4/14	9/11
Birth weight (g)	1064 ± 203	1089 ± 219	1010 ± 160	1108 ± 231	1060 ± 239	1005 ± 137
Gestational age (week)	29.0 ± 1.3	29.0 ± 1.1	28.0 ± 1.5	28.0 ± 1.4	28.7 ± 1.8	28.2 ± 1.0
BPD	6 (20%)	2 (10%)	6 (29%)	3 (16%)	9 (50%)	7 (35%)
PROM	8 (28%)[a]	3 (16%)[a]	7 (33.3%)	3 (16%)	6 (33%)	2 (10%)
IVH	15 (52%)	8 (42%)	11 (52%)	11 (58%)	6 (33%)	8 (40%)
RDS	20 (69%)	10 (53%)	15 (71%)	14 (74%)	12 (67%)	14 (70%)
PDA	13 (45%)	5 (26%)	8 (38%)	8 (42%)	14 (78%)[e]	8 (40%)[e]
Sepsis–NEC	3 (10%)[b]	6 (32%)[b]	4 (38%)	8 (42%)	7 (39%)	7 (35%)
Preeclampsia	9 (31%)	6 (32%)	2 (10%)	5 (26%)	2 (11%)	3 (15%)
Twin pregnancy	5 (17%)[c]	1 (5%)[c]	3 (14%)[d]	14 (74%)[d]	9(50%)	6 (30%)
p value	[a]0.03, [b]0.04, [c]0.005		[d]0.001		[e]0.001	

CG control group, *PTG* propranolol treatment group, *ROP* retinopathy of prematurity, *BPD* bronchopulmonary dysplasia, *PDA* patent ductus arteriosus, *PROM* premature rupture of membranes, *IVH* intraventricular hemorrhage, *RDS* respiratory distress syndrome, *NEC* necrotizing enterocolitis

Table 2 External interventions and study results in stage 0 ROP study groups

Study groups (*n*:48)	External interventions					Results	
	Use of antenatal steroid (*n*:36) (%)	Number of blood transfusion in the first phase (median ± SD)	Number of blood transfusion in the second phase (median ± SD)	Duration of ventilator treatment (h (median ± SD)	Use of oxygen (day) (median ± SD)	Plus disease detection in retinal examination	Increase in ROP stages (*n*:6) (%)
CG (*n*:29)	22 (76%)	1.24 ± 1.9	2.30 ± 2.4	262.0 ± 398.9	19.5 ± 21.0	1 (3%)	4 (14%)
PTG (*n*:19)	14 (74%)	0.85 ± 0.9	0.95 ± 0.9	127.2 ± 138.2	13.2 ± 14.5	–	2 (11%)
p value	0.12	0.39	0.02	0.15	0.32	0.41	0.37

ROP retinopathy of prematurity, *CG* control group, *PTG* propranolol treatment group

opening of membranes. Cases at stage 2 and above, according to Volpe scoring [15], were considered to be positive and recorded as intraventricular hemorrhage (IVH). Cases with a ratio of patent ductus arteriosus (PDA) and right atrium–aortic root over 1.4 were considered positive. Cases with necrotizing enterocolitis (NEC) and sepsis were recorded together. The Bell classification [16] was used for NEC. Patients who had received points above 5 by Töllner criteria [17] were recorded as positive for sepsis. Candida proliferation was observed in the blood culture of one patient each in the stage 0 ROP therapeutic group and stage 2 ROP CG.

Blood transfusion of 10 cc/kg was given to those cases in need.

Bradycardia was defined as cardiac rate below 100/min; apnea as respiratory arrest longer than 20 s together with bradycardia and saturation that had

Table 3 External interventions and study results in stage 1 ROP study groups

Study groups (*n*:40)	External interventions					Results	
	Use of antenatal steroid (*n*:22) (%)	Number of blood transfusion in the first phase (median ± SD)	Number of blood transfusion in the second phase (median ± SD)	Duration of ventilator treatment (h) (median ± SD)	Use of oxygen (day) (median ± SD)	Plus disease detection in retinal examination	Increase in ROP stages (*n*:17) (%)
CG (*n*:21)	12 (57%)	2.23 ± 2.1	2.23 ± 1.8	457.7 ± 659.5	27.5 ± 32.9	2 (10%)	10 (48%)
PTG (*n*:19)	10 (53%)	1.57 ± 1.0	1.52 ± 1.3	308.2 ± 419.6	20.0 ± 21.0	1 (5%)	7 (37%)
p value	0.56	0.23	0.21	0.40	0.40	0.60	0.49

ROP retinopathy of prematurity, *CG* control group, *PTG* propranolol treatment group

Table 4 External interventions and study results in stage 2 ROP study groups

Study groups (*n*:38)	External interventions					Results	
	Use of antenatal steroid (*n*:29) (%)	Number of blood transfusion in the first phase (median ± SD)	Number of blood transfusion in the second phase (median ± SD)	Duration of ventilator treatment (h) (median ± SD)	Use of oxygen (day) (median ± SD)	Plus disease detection in retinal examination	Increase in ROP stages and LPC (*n*:7) (%)
CG (*n*:18)	11 (6%)	1.77 ± 1.3	2.22 ± 1.6	674.6 ± 551.7	34.5 ± 25.3	4 (22%)	5 (28%)
PTG (*n*:20)	18 (90%)	1.60 ± 2.2	0.65 ± 1.08	462.0 ± 615.6	25.2 ± 29.0	2(10%)	1 (5%)
p value	0.03	0.77	0.001	0.27	0.29	0.15	0.02

ROP retinopathy of prematurity, *CG* control group, *PTG* propranolol treatment group, *LPC* laser photocoagulation

fallen below 88%; hypotension as mean arterial blood pressure less than the 10th percentile for gestation/birth weight and postnatal age. In our study, hypoglycemia was considered when blood glucose level decreased below 40 mg/dL [4]. Blood sugar was measured 2–4 times a day by means of peripheral capillary method in each subject. The cases in which hypoglycemia was detected were monitored more closely; sporadic hypoglycemia was not a reason for exclusion from the study.

In each stage of ROP, the cases were studied in terms of their gender, diseases likely to affect ROP, and their distribution between the groups based on their being in the CG or PTG with the purpose of determining statistical significance, if any, which could affect the study. Also studied was the absence or presence of statistical differences of birth weight, gestational age, and external interventions likely to affect ROP, between the CG and PTG. At the end of each table, the increase in ROP stage in the CG and PTG and the statistical significance of the differences between the groups are specified (Tables 1, 2, 3 and 4).

Exclusion criteria

Patients with cardiovascular anomaly, renal failure, apnea, hypoglycemia, and bradycardia, those who had not taken their medicine throughout the day, and those whose weight gains were not at the level desired were excluded from the study. In addition, some patients were also excluded from the study at their parents' request.

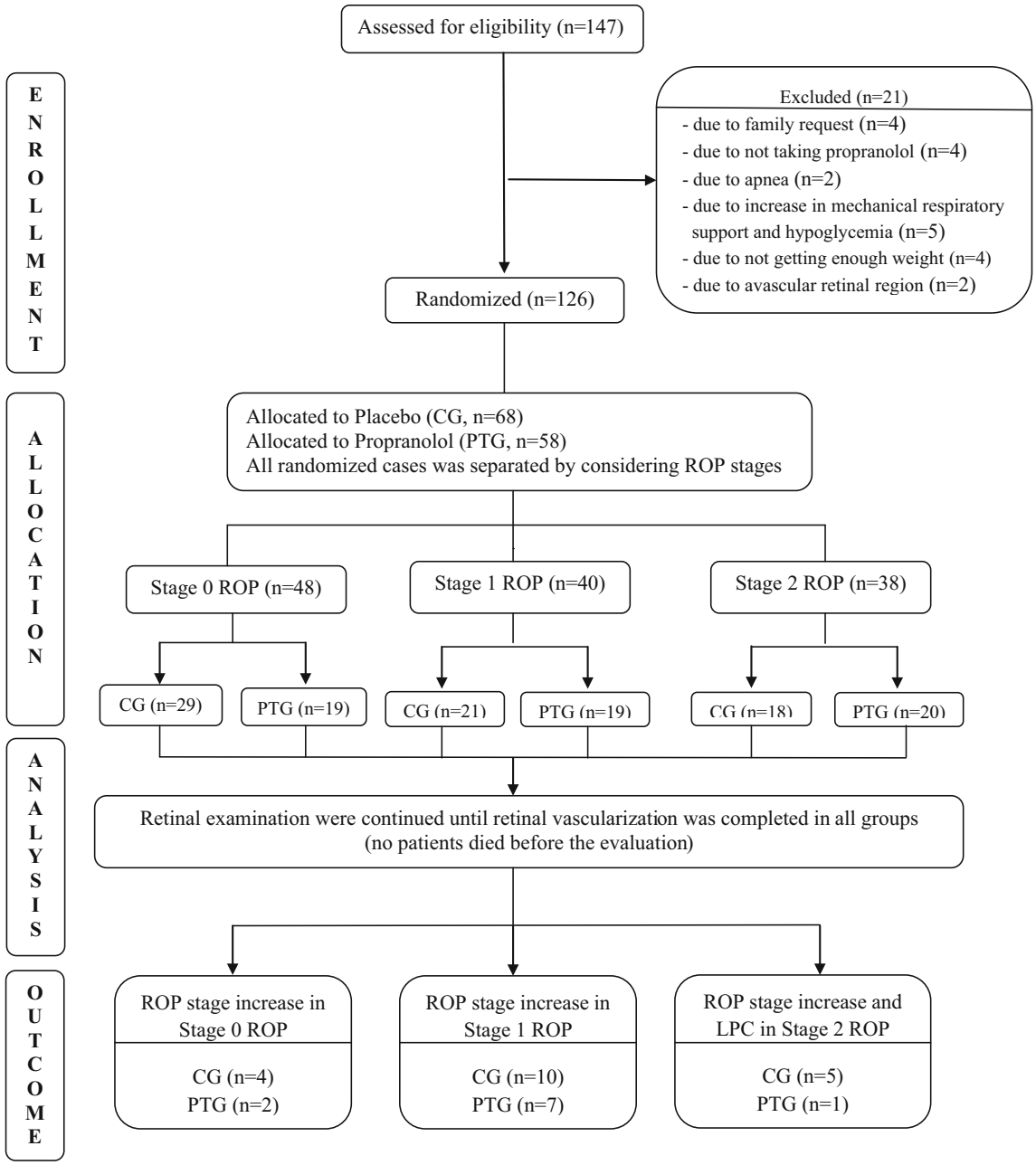

Fig. 1 Consolidated standards of reporting trials flow diagram; enrollment, randomization, and analysis of the 147 very preterm infants. *ROP* retinopathy of prematurity, *CG* control group, *PTG* propranolol treatment group, *LPC* laser photocoagulation

Statistical analysis

The data were analyzed by using the SPSS 16.0 (SPSS Inc. Chicago, Illinois) statistical package program. Distribution of the data was controlled via the Shapiro–Wilk normality test. Between groups, normally distributed variables were compared by using the independent sample *T* test. Variables without normal distribution were compared by using the Mann–Whitney *U* test. The chi-square test was utilized to analyze rational data. $p < 0.05$ was accepted as statistically significant.

Results

The distribution in the ROP groups of diseases that could affect ROP and the significance level of these distributions are presented in Table 1. There were statistically significant differences between the CG and PTG in terms of PROM ($p = 0.03$), NEC–sepsis ($p = 0.04$), twin pregnancy ($p = 0.005$) in stage 0 ROP cases, twin pregnancy ($p = 0.001$) in stage 1 ROP patients, and PDA ($p = 0.001$) in stage 2 ROP patients.

Table 2 presents the distribution of external interventions capable of affecting ROP of 48 patients in the stage 0 ROP group. In terms of external interventions, there was a significant difference between the CG and PTG when considered only from the point of view of blood transfusion given in the second phase ($p = 0.02$). When we studied the stage 0 ROP cases in terms of the study results, we saw increases in ROP stage in four of the 29 cases (14%) in the CG. Two of these increases were to stage 2, and two to stage 1. ROP stage increases in the PTG were seen in two of the 19 cases (11%). Two of these increases also were to stage 1. While plus disease was detected in one patient (3%) in any period in the CG of stage 0, it was not detected in any period of the patients in the PTG of stage 0 ($p > 0.05$). The increases in the CG and PTG in stage 0 ROP did not reach statistical significance ($p > 0.05$) (Table 2 and Fig. 1).

Table 3 shows the distribution, according to the CG and PTG, and external interventions that can affect ROP of the 40 cases in the stage 1 ROP group. In the cases in these groups, there was no difference between the CG and PTG statistically significant enough to affect the study ($p > 0.05$). The examination of the study results of the increases in ROP stages in the patients of the stage 1 ROP group revealed that increases in ROP stage were seen in ten of the 21 cases (48%) in the CG and in seven of the 19 cases (37%) in the PTG. All of the stage increases in these patients were to stage 2, and they did not reach statistical significance ($p > 0.05$). In addition, plus disease was detected in two patients (10%) in any period in the CG of stage 1; it was detected in one of the patients (5%) in the PTG of stage 1 ($p > 0.05$) (Table 3 and Fig. 1).

Table 4 shows the distribution, according to the CG and PTG, and the external interventions that can affect ROP of the 38 cases in the stage 2 ROP group. However, there was a statistically significant difference because of the blood transfusion in the second phase and antenatal steroid use ($p = 0.001$ and $p = 0.03$). In this stage of CG, plus disease was detected in four (22%) patients in any period, whereas the number of the patients with plus disease detected in any period in the PTG of the stage 2 was two (10%) ($p > 0.05$). The ROP stage increases in stage 2 ROP cases were observed in five of the 18 cases (28%) in the CG and in one of the 20 cases (5%) in the PTG, the difference being significantly different ($p = 0.02$) (Table 4 and Fig. 1).

The cases we took away from our work

Throughout the study, two cases in stage 0 ROP study group (one CG and one PTG) and one case in stage 1 ROP study group (CG) were removed from the study upon the request of their families. In stage 2 ROP study group (PTG), however, the number of the cases removed from the study at the request of their families was one patient. Two cases in stage 0 ROP study group (PTG) and two cases in stage 1 ROP study group (PTG) were removed from the study on the 38th and 42nd, and 31st and 45th days, respectively, because they had not taken their medicine throughout the day. There was no case removed from the study in stage 2 ROP study group since no patient disrupted their treatments. A total of four patients in stages 1 (CG) and 2 ROP study group (PTG) were excluded from the study between the week 4 and 10, because it was realized during their follow-up that they failed to achieve the weight increase desired (Fig. 1).

Two cases in stage 0 ROP study group (CG and PTG) were removed from the study on their 8th and 12th treatment day. Similarly, two cases in stage 1 ROP study group (PTG) were removed from the study on the 11th and 13th treatment day because of their increasing ventilator need, and three cases in stage 2 ROP study group (one CG and two PTG) had to be withdrawn from the study on the 4th, 5th, and 18th treatment day because of hypoglycemia and increasing ventilator need (Fig. 1).

Since there was avascular retinal field available in their retinal examinations, both of the two cases in stages 0 and 1 ROP study group (one CG and one PTG), they underwent LPC. These two patients were excluded from the study. Since none of the patients in stage 2 ROP study group had avascular retinal field, they did not get LPC (Fig. 1).

Discussion

At the present time, in parallel with the increasing incidence of premature births, the diseases associated with them have also increased. The most important of these diseases is ROP [1]. In our clinical study, propranolol, which has shown some positive effects on ROP in oxygen-induced retinopathy (OIR) studies [2, 3], was considered and applied to cases of ROP in various stages (stages 0, 1, and 2). In our study, it was observed that propranolol, while not providing satisfactory benefit in cases with early-stage ROP (stages 0 and 1), proved to be considerably beneficial in advanced stage ROP (stage 2) in very preterm infants.

Plus disease is the most important pathology in ROP monitoring, because its presence during retinal examination is an ominous sign for progressive ROP. In practice, treatment decisions almost always are based on the presence or absence of plus disease. The presence of plus disease was an important criterion for treatment decisions, as defined by the Cryotherapy for Retinopathy of Prematurity (CryoROP) study. In addition, the findings of the Early Treatment of ROP (ETROP) study have also emphasized further the priority of plus disease [12, 13]. When we considered plus disease, the most important study group among our study groups was stage 2 ROP study group. There was a numerical difference between CG and PTG in this study groups in terms of plus disease, but no statistical significance was found for this difference. In our study, however, the number of plus diseases and the number of patients requiring LPC were numerically parallel to each other. Propranolol may also be considered to reduce plus disease as the LPC requirement is reduced. However, in order to be able to say this, there is a need for studies with a larger number of patients.

Relative excess use of oxygen support in preterm babies is one of the most important factors encountered at the beginning of ROP. The vascular autoregulation in preterm newborns is very different from that in mature newborns. While in mature cases retinal blood flow occurs within a wide range of perfusion pressure, it occurs in a narrow range of pressure in preterm infants, which in turn renders preterm cases more vulnerable to the pernicious effects of oxygen [5, 18]. There was no statistically significant difference between the study groups in terms of oxygen use in our study. For this reason, evaluation of the efficacy of propranolol on ROP could be done more objectively.

The beneficial effects of β-blockers have been seen in adult macular degeneration [19]. Animal studies (OIR) in previous years have revealed the effects of the β_2-AR on ROP [3]. The data obtained from these studies have demonstrated that hypoxia-induced neovascularization can be reduced by blocking the β_2-AR [2]. This regression of neovascularization is realized by β_2-AR localized on retinal cells since β_2-AR in these cells has an important effect on the regulation of VEGF [3]. The results of these OIR constituted the basic idea of our study.

The current approach to ROP pathogenesis is the biphasic theory [20]. According to this theory, ROP is a disease consisting of two stages, known as phase 1 and phase 2. The retina, as a result of preterm birth, is exposed to a relatively hyperoxic environment and low stability, which disrupt (normal vascularization slows down and even stops) normal vascularization function (phase 1). Later, however, there appears too weak but excess vascularization developing in response to phase 1, and this event is the main reason for the start of phase 2. That is, the stopped vascularization (phase 1) begins to grow excessively through mediators such as VEGF, insulin-like growth factor 1 (IGF-1), and in the end, this causes the protein to leak out of the vessel and fibrous scar formation and retinal detachment develops (phase 2) [4–7, 20, 21].

These two phases are the mirror image of each other. Phase 1 lacks mediators, unlike phase 2 which abounds with them. While phase 1 inhibits vascularization, phase 2 is characterized by abnormal proliferation of blood vessels [4–7, 20, 21].

We tried to demonstrate the efficacy of propranolol on ROP by administering it at the beginning of phase 2 to prevent neovascularization and to inhibit phase 2. In our study, we emphasized the above-mentioned phase concept, which constitutes the basic pathology of ROP. This was due to the suppressive effect of propranolol on VEGF [22]. Because our aim is to lower the elevated VEGF levels, we took care of propranolol treatment in the second phase of ROP, which is increased VEGF levels. The second phase of ROP was already the phase that created the essential pathology that caused it to occur. If propranolol is administered in the first phase of ROP, the VEGF levels that have already fallen during this phase may

be further reduced. As a result, this event may lead to further exacerbation of the second phase (neovascularization phase) of the ROP.

For this reason, we took care of propranolol treatment at the end of the first phase of ROP and at the beginning of the second phase [1, 4–7, 10]. It is suggested that particularly postmenstrual age be considered in determining the phases of ROP and timing retinal examination. The period before the 32nd postgestational week is in agreement with the first phase of ROP. This period is in agreement with the time of the first retinal examinations of the newborn patients at risk of ROP [1, 4, 5, 10]. In this way, we tried to take advantage of the suppressive effect of propranolol on the vessels during the neovascularization period (second phase).

The effects of blood transfusion on ROP have been discussed in many studies. The relative hypoxia caused by anemia may increase retinal hypoxia and stimulate vasoproliferation in second phase of ROP. Blood transfusion can reduce this effect [23]. In fact, this idea is compatible with the logic of our work. In our study, blood transfusion was higher in CG group during the second phase of ROP. In this case, CG was advantageous but PTG was disadvantageous. Despite this current situation, it was observed that the propranolol reduced LPC requirement in the PTG of stage 2 ROP in our study group. If studies can be made that CG and PTG are compatible with each other in terms of blood transfusion, the efficiency of propranolol on ROP may be found more meaningful.

In recent years, it has been propounded that a phase in which the retina becomes more vulnerable to intrauterine fetal inflammation plays an important part in the pathogenesis, and this phase has been called the pre-phase. It is thought that in this phase antenatal factors such as infection and inflammation render the fetal retina vulnerable to ROP [24]. Therefore, infections in the antenatal period are important. The most important of these is the PROM. PROM was found to be increased in CG of stage 0 ROP patients. In terms of postnatal infections (such as NEC and sepsis), the outcomes of PTG cases were found increased. In our study, we excluded the patients with clinical findings such as renal failure, apnea, hypoglycemia, bradycardia, and increased need for mechanical ventilation. The PROM, NEC, and sepsis patients in our study had normal general conditions and so no deterioration in their clinical and general condition was observed. In conclusion, we think that the clinical pathologies that we mentioned above do not affect the results of our study.

There was a statistically significant difference only in the cases of stage 2 ROP study group in terms of antenatal steroid use. There are authors who claim that the use of antenatal steroids is the therapeutic effect of ROP [23]. However, there are authors who claim that the use of antenatal steroids has no effect on ROP [25]. That is, the effect of antenatal steroid use on ROP is not clear. In this regard, it can be assumed that the use of antenatal steroids is not a factor that affects the outcome of our study.

In the current study, the desired regression was not achieved in PTG in stages 0 and 1 ROP cases. As was demonstrated in previous OIR studies, these findings can be ascribed to the fact that the retina remains more hypoxic in stage 2 ROP cases and that beta-blockers are more effective in such cases. This, in turn, is a desired feature for normal tissues (normoxic tissues) in terms of the reliability of beta-blockers. Nevertheless, since ROP is a disease of premature infants, its usage at this age raises certain concerns. These justifiable concerns include the potential effects of VEGF blockage on the development of other vital organs [26]. However, studies have shown that propranolol is effective on VEGF in hypoxic rather than in normoxic retinas. In short, as has been demonstrated in certain animal studies, β_2-AR blockage does not affect VEGF levels in the brain, lungs, liver, and heart in newborns, because these tissues are more normoxic than the retinas in preterm infants [2–4, 27, 28]. However, in order to avoid the potential adverse effects of propranolol, propranolol-containing eyedrops have come to the fore. In studies of mice OIR model, it was observed that the eyedrops containing 2% propranolol was effective on retinal neovascularization. However, the effect was mostly obvious on superficial neovascularization but limited on deep retinal plexus. In addition, it has been reported in recent studies that the use of propranolol as eyedrops is effective in preventing ROP and is more reliable than its being used orally as well as being practical and cheap [29, 30].

The efficacy of propranolol in stage 0 and stage 1 ROP was statistically insignificant; however, propranolol stops the progression of the disease in stage 2 ROP cases, preventing LPC. The cause of this difference in the efficacy of propranolol may be

considered to be that the retinal tissue with the advanced stage is more hypoxic, therefore, the efficacy of propranolol to be more selective for these tissues. However, this idea may be answered after extensive studies at the tissue level.

Study limitations

This study on the effects of propranolol on ROP was limited to 126 cases and, owing to technical reasons, VEGF levels in the cases could not be studied, which is the most important shortcoming of our study. Increasing the number of cases and close observation of blood VEGF would yield healthier and clearer conclusions in ROP cases. However, it is important that our study covered the effects of propranolol not only on advanced but also on lower stages.

Conclusion

Our study showed that the second-phase propranolol therapy in the early stages of ROP, like stage 0–1, has little effect on the development of ROP, unlike second-phase propranolol therapy in advanced stages of ROP, like stage 2, which has positive effects on the development of ROP.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

Informed consent This study was approved by the Erciyes University ethical committee, Turkey. Written informed consent was obtained from the parents.

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