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Short-term Refractive Effects of Propranolol Hydrochloride Prophylaxis on Retinopathy of Prematurity in Very Preterm Newborns

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ABSTRACT
Purpose: Retinopathy of prematurity (ROP) is one of the major problems of surviving premature infants with several ophthalmic morbidities such as increased risk of refractive errors, strabismus, and cortical visual impairment. Use of propranolol hydrochloride (PH) for the prevention of ROP is a new promising treatment modality. However, long-term effects are still to be defined. In our study, we aimed to investigate the short-term refractive effects of PH used for ROP prophylaxis in very preterm newborns.
Methods: This is a prospective, randomized, double-blind, placebo-controlled study. Very preterm newborns with a birthweight less than or equal to 1500 g and/or born prior to 32 gestational weeks were included in the study. The subjects were randomly divided into two groups: control group (CG, n = 37) given placebo and PH group (PHG, n = 34) given PH starting from 4 weeks after birth (27.1 ± 2.1 day). PHG patients received PH therapy for about 1 month (25.7 ± 7.8 day). Anthropometric measurements including weight, length, and head circumference were recorded before PH treatment (at birth) and during eye control (at corrected age). Cycloplegic refraction values were measured by retinoscopy at corrected age (CG: 10.3 ± 4.3 months, PHG: 11.4 ± 4.8 months).
Results: Anthropometric measurements including gestational age, weight, length, and head circumference were similar at birth and corrected age in both groups. The mean level of spherical refraction was significantly less hyperopic in the PHG than in the CG (CG: 1.37 ± 1.40 D, PHG: 0.37 ± 1.44 D) (p = 0.005).
Conclusion: PH may lead to myopic shift by affecting the beta-adrenergic receptors in the choroid or ciliary body of the developing eye. Long-term refractive follow-up is required in order to elucidate the effects of PH on emmetropization process of these very preterm infants.

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Propranolol hydrochloride; retinopathy of prematurity; short-term refractive effects; very preterm newborns

Introduction

Propranolol hydrochloride (PH) is a non-selective (both β1 and β2) beta-adrenoreceptor (β-AR) blocker which is increasingly used to treat a multitude of diseases in the neonatal period such as cardiac and endocrine problems, benign vascular neoplasms.[1–6] Apart from the aforementioned uses, PH has recently come to the fore, especially in treating retinopathy of prematurity (ROP). PH has been shown to have positive effects in the treatment of ROP in studies done so far on this subject.[1,7]

Although the acute effects of PH treatment on the development of ROP have been presented in the above-mentioned studies, no data is available regarding the short- and long-term effects of systemic PH treatment on the developing eye and body of the very preterm infant. As the neonatal period is a very sensitive period in a developing premature infant, systemic drugs blocking widely expressed receptors must be carefully evaluated in order to completely determine its systemic effects. In the present study, we aimed to investigate the short-term effects of PH treatment both on the development of very premature infant eye and on somatic development parameters. As a continuation of our previous trial[1] on the effects of PH treatment on development of ROP, the present study aimed to compare the somatic development parameters and refractive status of infants receiving PH with infants receiving placebo.

Methods

This study was done by evaluation of the refractive status and somatic development parameters of the infants enrolled in our previous study[1] done on the effects of PH treatment on development of ROP. To be mentioned briefly, it was a randomized, double-blind, placebo-controlled study which included a total of 171 cases in the neonatal intensive care unit of the Erciyes University School of Medicine.[1] The study was approved by the institutional ethics committee, and informed consent was obtained from the parents of all patients.

In our initial study,[1] 205 patients at risk of ROP development, with gestational age < 32 gestational weeks and gestational weight < 1500 g, were enrolled and randomized into propranolol hydrochloride group (PHG) and control group (CG) to receive PH and distilled water, respectively. PH treatment was started at around 1 month after birth (27.1 ± 2.1 days) and was given until the risk of ROP was averted (25.7 ± 7.8 days). The patients in the CG received distilled water in the same period for a month (Table 1).

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Table 1. Duration and initiation time of PH therapy and anthropometric data of the patients in this period.

	CG n = 37 (mean±SD)	PHG n = 34 (mean±SD)	p-value
Gender (male/female)	17–20	13–21	-
Gestational age (weeks)	29.1 ± 1.4	28.7 ± 1.5	0.37
Birth weight (g)	1192.1 ± 226.2	1142.0 ± 245.1	0.37
Birth height (cm)	37.7 ± 2.8	36.3 ± 3.3	0.60
Birth head circumference (cm)	27.0 ± 1.9	26.7 ± 3.4	0.20
PH treatment initiation time (days)	–	27.1 ± 2.1	–
PH treatment duration (days)	–	25.7 ± 7.8	–

CG, control group; **PHG**, propranolol hydrochloride group; **PH**, propranolol hydrochloride.

PH was prepared by dissolving 40 mg Dideral tablets (Sanofi-Aventis) in 20 mL distilled water. It was administered orally or with an orogastric tube 30 minutes prior to feeding times. It was started in low doses (0.2 mg/kg/6 h) and gradually increased to therapeutic doses (0.5 mg/kg/6 h) on the third day in order to avoid acute side effects of PH treatment.

ROP screening was done by an experienced ophthalmologist specialized in retinal diseases. The decision to discontinue PH treatment was given according to the status of retinal vascularization (PH was discontinued when the retinal vascularization reached into zone 3 or failed to pass beyond posterior zone 2).

In our study, bradycardia was defined as the cardiac rate falling below 100 per minute, apnea as the cessation of respiration longer than 20 seconds with an accompanying bradycardia and saturation below 88%, and hypotension as the mean arterial blood pressure less than the 10th percentile for birth weight and postnatal age.[8] Detection of bradycardia, apnea, and hypotension twice at different occasions or detection of persistent bradycardia, apnea, and hypotension for once were considered to be reasons for exclusion from the study. Blood glucose <40 mg/dL was considered as hypoglycemia.[9] Patients on PH treatment were hospitalized and their blood sugar levels were measured 2–4 times a day using peripheral capillary method. The cases in which hypoglycemia was detected were monitored more closely for blood glucose level than those without hypoglycemia. Cases with sporadic hypoglycemia were not excluded from the study. The medication of patients in the PHG was started in their hospitalization period. The medication of patients who were discharged from the hospital but were still at risk of ROP was continued at home by their parents.

Of the patients we managed to contact and were included in our current study, 37 received distilled water and thus, were assigned to the CG, while the remaining 34 patients received PH and were assigned to the PHG. They were brought to hospital for a somatic check-up and ophthalmological examination in particular. Somatic development parameters (height, weight, head circumference) were recorded at birth and at the corrected age (Tables 1 and 2). Refractive status was evaluated by a masked experienced ophthalmologist through cycloplegic retinoscopy with 1% cyclopentolate, and spherical equivalents were determined at the corrected age. The right eye of each subject was used for data analysis (Tables 2 and 3).

Table 2. Time of eye control and anthropometric data of the patients in this period.

	CG n = 37 (mean±SD)	PHG n = 34 (mean±SD)	p-value
Corrected age during eye control (months)	10.3 ± 4.3	11.4 ± 4.8	0.17
Weight during eye control (g)	8109.4 ± 1562.5	8092.6 ± 1951.2	0.97
Height during eye control (cm)	69.1 ± 6.0	70.5 ± 7.6	0.37
Head circumference during eye control (cm)	41.8 ± 2.7	42.3 ± 2.5	0.50

CG, control group; **PHG**, propranolol hydrochloride group.

Table 3. Refraction measurement results.

	CG n = 37 (mean±SD)	PHG n = 34 (mean±SD)	p-value
Spherical equivalent (D)	1.37 ± 1.40	0.37 ± 1.44	**0.005**

CG, control group; **PHG**, propranolol hydrochloride group; **D**, diopter.

Exclusion criteria

The cases with sepsis, renal failure, small gestational age, bronchopulmonary dysplasia, apnea, central nervous system disorders, hypoglycemia, hypoxia, nutritional intolerance, and assisted mechanical ventilation were excluded from our initial study.[1] Of the 205 eligible newborns enrolled in our first study, 34 cases were lost to follow-up during the study period and the study was completed with 171 cases. The reasons for dropping out from the study were as follows: families' desire to be excluded from the study (CG:-, PHG:6), irregularities in taking medicine (going without medicine for 24 hours) (CG:-, PHG:13), increasing need for mechanical ventilator-apnea-bradycardia-patent ductus arteriosus (PDA) (CG:-, PHG:2), increasing need for mechanical ventilator-sepsis-PDA-hypotension-hypoglycemia (CG:2, PHG:5), arrest in retinal vascularization (CG:2, PHG:1), and anti-VEGF treatment (CG:2, PHG:1).

Of the 171 cases who were taken into analysis in our initial study,[1] 100 cases could not be included in our second study due to the following reasons: failure to access to the patients' electronic health records (CG:6, PHG:6), moving out to another city (CG:7, PHG:9), changes in contact information (CG:14, PHG:8), lack of interest by the patients' family (CG:6, PHG:8), failure to obtain reliable refractive examination (CG:5, PHG:6), failure to achieve coordination with the patients' families owing to socio-economic reasons (CG:9, PHG:7), patients' records kept erroneously by researchers (CG:1, PHG:1), and domestic problems (CG:3, PHG:4).

Statistical analyses

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 using the independent sample t-test; variables without normal distribution were compared applying the Mann–Whitney U test. The chi-square test was used to analyze rational data. A p-value of <0.05 was accepted as statistically significant.

Results

The study group consisted of 71 patients, 37 of whom received distilled water and 34 received PH treatment. Baseline characteristics and anthropometric measurements are presented in Tables 1 and 2. Gestational age (29.1 ± 1.4 weeks, 28.7 ± 1.5 weeks), gestational weight (1192.1 ± 226.2 g, 1142.0 ± 245.1 g), gestational height (37.7 ± 2.8 cm, 36.3 ± 3.3 cm), and head circumference (27.0 ± 1.9 cm, 26.7 ± 3.4 cm) values were similar between the study groups (p > 0.05, Table 1).

Cycloplegic refractions values, as well as weight, height, and head circumference during eye control were measured at similar corrected ages (10.3 ± 4.3 weeks, 11.4 ± 4.8 weeks). The weight (8109.4 ± 1562.5 g, 8092.6 ± 1951.2 g), height (69.1 ± 6.0 cm, 70.5 ± 7.6 cm), and head circumference (41.8 ± 2.7 cm, 42.3 ± 2.5 cm) measured during refractive evaluation were similar between the study groups (p > 0.05, Table 2). However, in terms of refractive values, the subjects in the PHG were significantly less hyperopic compared to those in the CG (CG: 1.37 ± 1.40 D, PHG: 0.37 ± 1.44 D) (p = 0.005, Table 3).

Discussion

Although the effects of systemic PH treatment have been addressed in a number of studies, few reports are present regarding the short- and long-term effects of PH on developing eye and developing infant.[1,7,10–15] Our study is one of the first studies to evaluate the short-term effects of PH treatment on refractive status and somatic development parameters of the very premature infants.

In our study, no difference was observed for somatic developmental parameters between the PHG and CG. Similar to our study, PH treatment has been shown to have no negative effect on growth and somatic development of newborn infants in a limited number of studies.[16] However, when it comes to refractive outcomes, there were significant differences between the two groups in our study.

Beyond somatic development, PH treatment can also have deleterious effects on the vital functions of the premature infant. In some studies, PH treatment has been found to be associated with hypotensive episodes within 48 hours of treatment initiation.[12] In our study, four cases were excluded due to occurrence of persistent hypotensive episodes in the first two days of PH initiation. The underlying causes for the development of these hypotensive episodes turned out to be secondary to underlying diseases such as PDA and sepsis rather than PH treatment. In our series, sporadic low pressure values and bradycardia were also encountered, though in small numbers and in limited degrees. Some studies recommend the PH treatment to be started in low doses in order to decrease the occurrence of hypotension and bradycardia.[12,17]We believe that the low incidence of the side effects in question can be ascribed to incremental (gradually) increasing of the dosage at PH treatment initiation.

In this study, we found that PH-treated infants had a lower level of hyperopia (0.37 ± 1.44 D) compared with the infants receiving placebo (1.37 ± 1.40 D) at corrected age. Normally, infants are expected to have significant amount of hyperopia at birth which decreases with maturation of the infant.

In the study done by Mutti et al,[18] average spherical refractive error decreased from +2.16 D at 3 months to +1.36 D at 9 months. The distribution of refractive error (measured by standard deviation) also decreased between 3 and 9 months (1.30 D compared with 1.06 D, respectively).[18] With emmetropization process, coordinated changes occur in the axial length, lenticular, and corneal power in order to bring the eye closer to emmetropia. Emmetropization occurs at an increased pace during the first year of life and then continues at a slower rate up to 6 years of age.

In the study done by Sanghvi et al,[19] visual outcomes of infants receiving PH were compared with those of infants receiving placebo at 1 year. Refractive outcomes of hyperopia greater than 3 diopters and any level of myopia (0 D >) were accepted as significant, mean refractive errors were not given. No difference was observed between study (18.42%) and control groups (23.8%) regarding rate of refractive error development. In that study, laser and anti-VEGF treatment rate was very high among groups (>25% PHG, >46% CG) which would affect the overall refractive development of the infants. In contrast, we were able to observe the effects of PH treatment more clearly as our groups did not include infants with previous treatment that might interfere with refractive development.

ROP is a significant risk factor for the development of myopia which is proportional to the severity of ROP.[20,21] Prematurity itself even in the absence of ROP may also result in development of myopia called myopia of prematurity due to arrested development of the cornea and lens.[22] In our study, the subjects were randomly assigned to the study groups, had similar baseline characteristics, and no case of advanced ROP requiring laser or intravitreal anti-VEGF therapy was encountered in any of the groups, therefore, ROP, prematurity, or other baseline characteristics cannot be used as an explanation for the difference in the refraction status between the CG and PHG. A likely mechanism for the explanation of the difference in the refractive status can be the effects of PH treatment on the developing eye. All types of β-ARs are present in the mammalian choroid, whereas retinal distribution is more controversial.[14,23,24]

The sympathetic nervous system exerts its effects primarily over the choroidal circulation as the retinal circulation does not receive direct autonomic control and is regulated primarily by local factors.[25] Choroidal circulation receives 80–95% of ocular blood flow with one of the highest blood flow rates in the body. The autonomic nervous system influences the choroidal blood flow through vascular smooth muscle control, where parasympathetic stimulation leads to selective vasodilatation in the anterior choroidal vessels and sympathetic stimulation produces widespread vasoconstriction throughout the choroid.[26]

Changes in the choroidal blood flow, vascularity, and/or production of glycosaminoglycans that osmotically draw water into lymphatic lacunae have been speculated as causative mechanisms. Inhibition of scleral proteoglycan synthesis regulating the rate of ocular elongation through choroid-originated molecules has also been proposed.[27]

We found that the infants in the PHG had a lesser degree of hyperopia than those in the CG. This difference can be due to the effects of systemic PH treatment over choroidal vessels and/or synthesis of molecules affecting the scleral structure. Increased choroidal thickness due to β-AR blockage might bring the retina to a more anterior position decreasing the level of hypermetropia. As we did not study the choroidal thickness in our study groups, this remains as a speculation and needs to be evaluated by optical coherence tomography (OCT) studies.

Another mechanism for this difference can be the effects of β-AR blockage on ciliary muscle. Ocular accommodation is primarily controlled by parasympathetic innervation of the ciliary muscle; however, supplementary inhibitory sympathetic innervation is also present. Sympathetic inhibition (mediated through β2-ARs) is slow in nature and small in amount (>40 seconds, <2D, respectively).[28,29]

Sympathetic inhibition requires presence of parasympathetic (accommodative) activity to function; it has no activity in the absence of accommodation.[28] Accommodation response starts to develop around the 6th month after birth which precludes sympathetic innervation to have activity in the newborn infant, thus decreasing the likelihood of PH to have an effect on accommodation. In addition, topical timolol maleate 0.5% treatment has been shown to exert no significant effect on the rate of myopia development in young school children studied over a 2-year period.[29,30]

Limitations of the study

We were able to enroll in our study only 71 patients we followed previously. Enlargement of study groups in future trials may provide more accurate data relevant to the topic. In addition, if somatic development tests can be repeated in subsequent corrected ages, more concrete data can be obtained on the visual function of preterm infants with a history of PH treatment.

Conclusion

We did not perform axial length, choroidal thickness, corneal or lenticular power measurements, determination of which would be valuable to highlight the real basis of the difference in refractive errors. Although systemic PH therapy for the treatment of ROP promises an alternative treatment for ROP, possible effects on emmetropization process, choroidal thickness, or axial length should be carefully studied in order to elucidate more fully the effects of this treatment modality.

Disclosure statement

No potential conflict of interest was reported by the authors.

Informed consent

Informed consent was obtained from all parents of patients who participated in this study.

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