Oral Propranolol for Retinopathy of Prematurity: Risks, Safety Concerns, and Perspectives

Luca Filippi, MD[1], Giacomo Cavallaro, MD[2], Paola Bagnoli, PhD[3], Massimo Dal Monte, PhD[3], Patrizio Fiorini, MD[1], Gianpaolo Donzelli, MD[1], Francesca Tinelli, MD[4], Gabriella Araimo, MD[2], Gloria Cristofori, MD[2], Giancarlo la Marca, Pharm Sc[5], Maria Luisa Della Bona, Pharm Sc[5], Agostino La Torre, MD[6], Pina Fortunato, MD[6], Sandra Furlanetto, Pharm Sc[7], Silvia Osnaghi, MD[8], and Fabio Mosca, MD[2]

Objective To evaluate safety and efficacy of oral propranolol administration in preterm newborns affected by an early phase of retinopathy of prematurity (ROP).

Study design Fifty-two preterm newborns with Stage 2 ROP were randomized to receive oral propranolol (0.25 or 0.5 mg/kg/6 hours) added to standard treatment or standard treatment alone. To evaluate safety of the treatment, hemodynamic and respiratory variables were continuously monitored, and blood samples were collected weekly to check for renal, liver, and metabolic balance. To evaluate efficacy of the treatment, the progression of the disease (number of laser treatments, number of bevacizumab treatments, and incidence of retinal detachment) was evaluated by serial ophthalmologic examinations, and plasma soluble E-selectin levels were measured weekly.

Results Newborns treated with propranolol showed less progression to Stage 3 (risk ratio 0.52; 95% CI 0.47-0.58, relative reduction of risk 48%) or Stage 3 plus (relative risk 0.42 95% CI 0.31-0.58, relative reduction of risk 58%). The infants required fewer laser treatments and less need for rescue treatment with intravitreal bevacizumab (relative risk 0.48; 95% CI 0.29-0.79, relative reduction of risk 52 %), a 100% relative reduction of risk for progression to Stage 4. They also had significantly lower plasma soluble E-selectin levels. However, 5 of the 26 newborns treated with propranolol had serious adverse effects (hypotension, bradycardia), in conjunction with episodes of sepsis, anesthesia induction, or tracheal stimulation.

Conclusion This pilot study suggests that the administration of oral propranolol is effective in counteracting the progression of ROP but that safety is a concern. *(J Pediatr 2013;163:1570-7)*.

Despite progressive improvements in neonatal care, retinopathy of prematurity (ROP) remains the major cause of blindness and visual impairment in children in both developing and industrialized countries.[1] The incidence of the disease is closely related to birth weight and gestational age (GA): ROP is more severe and more frequent in extremely premature infants and in newborns with extremely low birth weights.[2]

The pathogenesis of ROP is hypothesized to consist of 2 distinct phases, of which the second phase is characterized by hypoxia-induced up-regulation of vascular endothelial growth factor (VEGF) and retinal neovascularization.[3] As understanding of the pathophysiology of ROP has increased, emphasis has shifted to selective therapies that target components of the angiogenesis cascade. There are some indications that the β-adrenergic system may interfere with ROP in infants. For instance, beta-adrenergic receptor (β-AR) polymorphisms existing in many black infants[4] may be responsible for the lower incidence of ROP progression in these infants compared with nonblack infants.[2,5] In fact, the polymorphism of G-protein–coupled receptor kinase (ie, GRK5-L41) facilitates β-AR phosphorylation, recruitment of β-arrestin, and consequent desensitization during catecholamine excess, making this population *genetically β-blocked*.[6] In addition, β-AR blockade with propranolol, a nonselective β_1-AR and β_2-AR blocker,[7] induced involution of infantile hemangioma,[8] the most common tumor of infancy that is often associated with ROP,[9] suggesting that β-AR blockers might be effective in ROP as well.

These observations are supported by experimental findings in a mouse model of oxygen-induced retinopathy (OIR),[10,11] where we demonstrated that retinal norepinephrine increases in response to hypoxia and β-ARs regulate VEGF production and retinal neovascularization.[12-14] Most interesting, these studies also

β-AR	β-adrenoreceptor
GA	Gestational age
OIR	Oxygen-induced retinopathy
ROP	Retinopathy of prematurity
VEGF	Vascular endothelial growth factor

From the [1]Neonatal Intensive Care Unit Medical Surgical Fetal-Neonatal Department, "A. Meyer" University Children's Hospital, Florence; [2]Neonatal Intensive Care Unit, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan; [3]Department of Biology, Unit of General Physiology, University of Pisa; [4]Department of Developmental Neuroscience, IRCCS Stella Maris, Calambrone, Pisa; [5]Department of Pediatric Neurosciences, "A. Meyer" University Children's Hospital; [6]Pediatric Ophthalmology, Careggi University Hospital; [7]Department of Pharmaceutical Sciences, University of Florence, Florence; and [8]Department of Ophthalmology, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

The authors declare no conflicts of interest.

Registered with ClinicalTrials.gov (NCT01079715), Current Controlled Trials (ISRCTN18523491), and European Union Drug Regulating Authorities Clinical Trials (2010-018737-21).

 http://dx.doi.org/10.1016/j.jpeds.2013.07.049

showed that significant reduction of neovascularization could be achieved by the administration of topical propranolol,[15] suggesting the therapeutic use of β-AR blockers to counteract retinal neovascularization in ROP.

Assuming in human preterm newborns with ROP that VEGF overexpression and retinal neovascularization in response to hypoxia might involve β-AR activation, we designed a randomized pilot trial to test whether the oral administration of propranolol in newborns with a precocious stage of ROP is safe and might reduce the progression of the disease.

Methods

We used the standard international classification to establish the location and severity of ROP.[16] A randomized controlled pilot trial was performed with preterm newborns with GA <32 weeks of age and Stage 2 ROP without plus in zone II who were admitted to 2 neonatal intensive care units, both regional reference centers for neonatal surgical diseases. Although infants were receiving supplemental oxygen, the target range of oxygen saturation was maintained between 91% and 95%. We randomized treated and control newborns with a 1:1 allocation in blocks of 8 by using a computer random number generator and stratified by center in 2 groups of GA 23-25 and 26-32 weeks; they alternated between propranolol added to standard treatment or standard treatment alone (the treatment adopted by the Early Treatment of Retinopathy of Prematurity Cooperative Group).[17] The allocation sequence was concealed in sequentially numbered, opaque, sealed envelopes. Exclusion criteria included newborns with congenital or acquired cardiovascular anomalies, renal failure or cerebral hemorrhage at enrollment, and newborns with ROP in zone I or at a more advanced stage than Stage 2 without plus in zone II. With severe adverse effects related to propranolol (severe bradycardia, hypotension, or wheezing), the administration of propranolol was permanently discontinued. If these episodes had been observed within the first 2 days of treatment, these newborns were included into the control group. The results were analyzed according to the per-protocol analysis. The study protocol was approved by the ethics committees of both centers. Written informed consent was obtained from the parents.

From February 2010 to May 2012, 56 newborns with ROP were identified. Three newborns with aggressive posterior ROP and one newborn with Stage 3 plus were excluded. Therefore, 52 newborns were enrolled, 26 in the treated and 26 in the control group (**Figure 1**; available at www.jpeds.com). One newborn who initially was enrolled in the treated group developed serious adverse effects from propranolol on the first day of treatment and was moved into the control group. Treated infants were randomized at 67 ± 14 days of postnatal age (weight 1678 ± 393 g), and the age of newborns in the control group was 68 ± 17 days (weight 1559 ± 431 g).

Demographic, obstetric, and comorbidities data were not different between treated and control patients (**Table I**). A total of 35 newborns (67.3%) were outborn, and most of them were transferred for surgery; 15 newborns in the treated group (57.7%) and 13 in the control group (50%) had at least one surgical intervention. Five newborns in the treated group and 2 in the control group had posthemorrhagic hydrocephalus that was treated with the placement of an Ommaya reservoir (CSF-Ventricular Reservoirs; Medtronic, Inc, Minneapolis, Minnesota) and then with a ventriculoperitoneal shunt implant.

The first 4 newborns in the treated group with a GA of 23-25 weeks and all the newborns in the older GA group were treated with 0.5 mg/kg/6 hours of propranolol (high dose). After the appearance of severe adverse events in 3 newborns in the 23-25 weeks' group, the dosage was reduced, and the remaining 8 newborns were treated with 0.25 mg/kg/6 hours (low dose). Newborns received propranolol for an average of 66.1 ± 31 days (range, 6-90 days): 60.2 ± 35 days (range, 6-90 days) in the 23-25 weeks group, 71.2 ± 28 days (range, 8-90 days) in the older group.

All newborns with GA <32 weeks had ophthalmologic evaluations through indirect ophthalmoscopy.[18] When ROP in zone II reached Stage 2 without plus, newborns were enrolled, and ophthalmologic examinations were scheduled weekly or more frequently, according to the severity of ROP. The RetCam Imaging System II (Clarity Medical Systems, Pleasanton, California) was used to monitor the progression of the disease. Propranolol was administered orally as a 2 mg/mL syrup shortly after feeding. The syrup was prepared by adding 0.2 g of propranolol hydrochloride powder to a 100-mL solution containing water for injections, sucrose 25 g, anhydrous citric acid 0.64 g, and sodium citrate tribasic dehydrate 0.2 g. The syrup is stable in amber glass bottles for at least 1 month at 2-8°C. The treatment was continued until complete development of retinal vascularization, although administration was not permitted for more than 90 days.

The physicians and nurses were aware of the allocated arm, but the ophthalmologists and data analyst were blinded to the allocation. When ROP reached Stage 2 or 3 with plus disease, the newborns were treated with peripheral retinal ablation performed by conventional laser photocoagulation with 810-nm diode laser (Iridis Quantel Medical, Clermont-Ferrand, France).[17] An intravitreal bevacizumab injection (Avastin; Roche, Basel, Switzerland) was considered as rescue treatment for more aggressive ROP with insufficient regression after laser treatment.[19] Laser photocoagulation and/or intravitreal bevacizumab were performed under general anesthesia (ketamine 1 mg/kg intravenously or fentanyl 4 μg/kg intravenously). Vitrectomy was considered in newborns with ROP Stage 4A to reduce tractional retinal detachment from fibrous proliferation.

Vital signs and respiratory and hemodynamic variables were monitored continuously (Infinity Delta; Dräger Medical System, Telford, Pennsylvania). Bradycardia was defined as a single heart-rate decrease below 100 bpm; apnea as a pause in breathing for more than 20 seconds or less when associated with desaturation, bradycardia, pallor, or reduced tone; and hypotension as mean arterial blood pressure less than the 10th percentile for gestation/birth weight and postnatal age.[20] Blood gas analysis, glucose, serum electrolyte levels, liver and renal function tests, complete blood cell count, and C-