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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

BRIEF REPORT

Treating infants with 0.2% propranolol eye micro-drops drastically reduced the progression of retinopathy of prematurity

Retinopathy of prematurity (ROP) continues to threaten the vision of premature infants. Premature exposure to an environment that is richer in oxygen than the uterus stops, or even regresses, retinal vasculature. This induces the first avascular phase of ROP, as confirmed by rodent models of oxygen-induced retinopathy. The second proliferative phase is reactive hypoxia-induced neovascularisation. Clinicians use defensive strategies to reduce the occurrence or progression of ROP, by preventing preterm deliveries and providing minimal oxygen support during the first weeks of life. Pharmacological approaches are currently poor. However, our team explored using unselective Beta 1/2 adrenoceptor antagonist propranolol during the proliferative phase of oxygen-induced retinopathy. This significantly reduced hypoxia-induced retinal neovascularisation by counteracting hypoxia-inducible factor-1 upregulation and the downstream proangiogenic cascade.[1]

Explorative clinical trials and three meta-analyses[2] showed that oral propranolol reduced ROP progression and the need for laser photocoagulation or anti-vascular endothelial growth factor treatment. However, this risked life-threatening complications in unstable preterm infants.[3]

Animal studies of oxygen-induced retinopathy,[1] found that eye micro-drops with 0.1% or 0.2% propranolol were safe, but only the 0.2% formulation decreased ROP progression.[4]

This study in the Neonatal Intensive Care Unit of the University Hospital of Pisa, Italy, aimed to provide further data on the impact of propranolol eye micro-drops on infants with early stages ROP. The medical records of all very low birth weight (VLBW) infants, born weighing <1500 g, with any stage of ROP were evaluated. We compared progression in patients admitted in 2010–2018, when no pharmacologic treatment was available, with patients admitted in 2019–2022 and treated with propranolol 0.2% eye micro-drops.

Propranolol administration was maintained until complete retinal vascularisation had been achieved or 90 days had elapsed. Ophthalmologists documented disease progression in both groups using the International Classification of ROP, Second Revision and recorded images using retinal cameras. The study was approved by the Pediatric Ethical Committee for Clinical Research, Tuscany region (number 52/2023), and informed consent was obtained from both parents.

There were 94/415 VLBW infants (22.7%) with ROP in 2010–2018 and 27/134 (20.1%) in 2019–2022 ($p = 0.544$). We excluded 13 historic controls who had been enrolled in previous trials with propranolol and two from the treatment groups with late ROP stage 1. The final study comprised 81 historic controls born at a mean gestational age of 27.4 ± 2.4 weeks and 25 treated patients born at a mean of 26.4 ± 2.0 weeks. The treatment group had a significantly lower birthweight ($p = 0.005$), and a higher incidence of respiratory distress syndrome ($p = 0.032$). They were more likely to receive medication for patent ductus arteriosus ($p = 0.024$) and red blood cell transfusions ($p = 0.027$).

Treated infants received three micro-drops of propranolol 0.2% (6 μL in each eye) every 6 h, delivered using a micropipette, followed by the compression of the nasolacrimal duct for 30 s. Just over a third (36%) began treatment when they had stage 1 ROP, while the others (64%) began it at stage 2. The average duration of treatment was 52.1 ± 21.5 days. No interruptions were reported.

No difference was observed in the progression to stage 2 ROP. However, there was a fourfold reduction in the number of treated infants who reached stage 3 when the treatment and control groups were compared ($p = 0.013$). The number needed to treat was 2.7 (95% confidence interval 1.761–6.215). A trend towards a reduction was also observed in the progression to stages 2–3 plus and to stage 4 (Figure 1). No adverse events were attributed to propranolol, namely severe hypotension, bradycardia, apnoea, bronchospasm, hypoglycaemia, local signs or rebound after treatment discontinuation.

Our study confirmed that 0.2% eye propranolol micro-drops were effective in breaking the link between hypoxia and vascular proliferation in ROP, although the results were probably underestimated. On the one hand, the start of treatment could be more uniformly anticipated at ROP stage 1, potentially reinforcing its efficacy. On the other hand, the groups compared in this study were not perfectly homogeneous, suggesting that the beneficial effects were obtained in a population with a higher risk of severe ROP.

Abbreviations: GA, gestational age; OIR, oxygen-induced retinopathy; ROP, retinopathy of prematurity; VEGF, vascular endothelial growth factor; VLBW, very low birth weight.

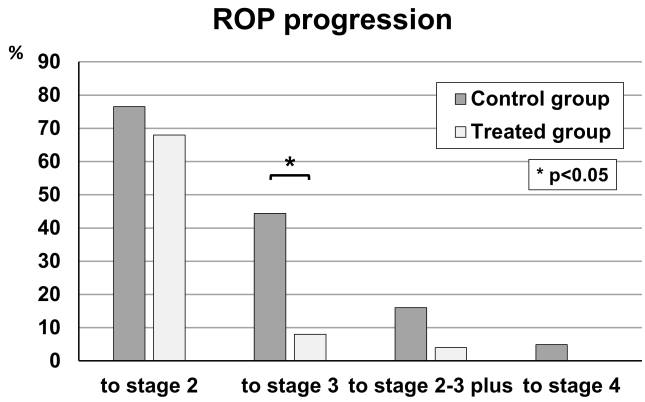

FIGURE 1 Progression patterns of very low birth weight infants with early-stage ROP treated with propranolol 0.2% eye micro-drops versus a historic control group that did not receive any treatment.

This secondary prevention approach is safe, very inexpensive and easily available and the absence of undesirable effects make it a useful tool for decreasing the progression of ROP. Importantly, this makes it suitable for even low-income countries.

Retinopathy of prematurity is predominantly considered a proliferative vascular disease. However, persistent vision impairments due to photoreceptors and post-receptor retinal neuron disorders observed in patients who had ROP suggest associations with neurosensory alterations.[5] Therefore, the availability of a drug with high cerebrospinal fluid permeability that interrupts the progression of ROP, protects retinal cells and prevents astrocyte degeneration[5] could provide neuroprotection.

Our study produced interesting results, but had some limitations. The treated cohort number was too low to draw definitive conclusions and higher doses of propranolol might increase treatment efficacy, without prejudicing safety and tolerability. The way that eye micro-drops are administered is not specifically designed for this purpose. Caregivers need training to administer the drug with acceptable accuracy and a more user-friendly system could ensure better results. Finally, retrospective, non-blinded studies may present bias and prospective randomised controlled trials are needed.

In conclusion, this study showed that treating infants with 0.2 propranolol eye micro-drops drastically reduced the progression of retinopathy of prematurity, but more studies are needed.

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CONFLICT OF INTEREST STATEMENT

None.

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