STUDY PROTOCOL

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Evaluation of timed dexamethasone eye drops to prevent proliferative retinopathy of prematurity: a study protocol for a randomized intervention, multi-centre, double-blinded trial (DROPROP)

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Abstract

Background As the survival rate of preterm infants continues to rise worldwide, more infants are at risk of developing sight-threatening retinopathy of prematurity (ROP). Destructive retinal laser treatment and intravitreal injections of anti-vascular endothelial growth factor (VEGF), factor, which have potential systemic side effects, are necessary to prevent blindness in severe cases of ROP. Off-label use in clinical settings suggests that dexamethasone eye drops, 1 mg/ml, may prevent the progression of ROP to severe disease (Type 1 ROP) requiring treatment. Our current study aims to assess the efficacy and safety of timely administered dexamethasone eye drops to reduce the need for laser or anti-VEGF ROP treatment in preterm infants.

Methods In a randomized prospective interventional, multi-centre, double-blinded trial, we plan to include 100 infants with severe ROP born before gestational age 30 weeks in Sweden. Infants will be randomized to intervention with dexamethasone eye drops (1 mg/ml) (n = 50) or placebo, saline (n = 50) until either ROP is resolved or severe ROP (Type 1 ROP) development occurs, fulfilling ROP treatment criteria. Eye drops will be administered one drop per day or every other day, depending on the severity of ROP, with a maximum duration of 12 weeks. The primary objective is to evaluate whether dexamethasone intervention reduces the proportion of infants developing Type 1 ROP compared to infants receiving a placebo. Adverse events and potential side effects will be recorded, such as high intraocular pressure and growth restriction. Levels of cortisol in saliva and glucose in urine will be measured repeatedly. Secondary outcomes will include the timing of ROP progression, the recurrence rate after ROP treatment and retinal morphology. An ophthalmological follow-up will be initiated at 2 and 5.5 years of age, evaluating visual acuity, refractive errors, strabismus, retinal morphology and ophthalmological complications. All outcomes in the study will be compared between the infants receiving dexamethasone intervention and those receiving placebo.

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Discussion Timely administration of dexamethasone eye drops may prevent severe ROP from progressing to Type 1 ROP, which requires treatment. This study aims to assess the efficacy and safety of dexamethasone intervention to support its clinical use and national guidelines.

Trial registration EudraCT, 2020–004933-19, registered in January 2021 and CTIS, 2023–505318-97–00, registered in August 2023.

Clinical trial number Not applicable.

Keywords Retinopathy of prematurity, Dexamethasone, Preterm infants, Eye drops

Background

Advancements in neonatal care have improved survival rates of preterm infants worldwide, leading to a growing number of infants suffering preterm-related morbidities [1-3]. Retinopathy of prematurity (ROP) is one of the leading causes of childhood blindness worldwide and primarily affects extremely preterm infants [4, 5].

In the initial phase of ROP, which occurs shortly after birth, blood vessel development in the retina is halted. During the next several weeks to months, the peripheral neural retina develops slowly and remains avascular. Increasing ischemia and inflammation in the avascular retina can lead to pathological neovascularization driven mainly by vascular endothelial growth factor (VEGF). In the worst-case scenarios, this neovascularisation leads to retinal detachment and blindness [6-8]. About 5-10% of ROP cases are severe enough to require treatment with retinal laser photocoagulation and/or with intravitreal anti-VEGF injections [4]. International guidelines regulate treatment indications based on ROP classification [9]. ROP is classified into ROP severity-stages (0 to 5) and retinal localization-zones (I to III) [10]. The presence of plus disease, tortuosity and dilation of central retinal vessels is a crucial sign for deciding the need for treatment. Severe ROP with indications for treatment (Type 1 ROP) is defined as any stage of ROP in zone I, with plus disease; ROP stage 3 in zone I, without plus disease; ROP stage 2 or 3 in zone II, with plus disease. Severe ROP requiring frequent follow-up but not fulfilling treatment criteria (Type 2 ROP) is defined as ROP stage 1 or 2 in zone I, without plus disease and ROP stage 3 in zone II, without plus disease [9]. Laser photocoagulation, which destroys the peripheral avascular retina, releasing angiogenic factors, helps reverse pathological vaso-proliferation. Laser treatment is often performed under general anaesthesia, which can be challenging for these vulnerable infants. Potential side effects after laser treatment are retinal haemorrhage, visual field loss, myopia, and retinal detachment [11]. Intravitreal injection with anti-VEGF can be performed under sedation, thereby avoiding the risks associated with general anaesthesia. However, intravitreal anti-VEGF agents enter the bloodstream, suppressing VEGF over an extensive period (ranging from weeks to months) with potential long-term systemic effects [12].

Dexamethasone is a synthetic glucocorticoid with antiinflammatory effects. It is widely used in adults to treat ocular surface and intraocular inflammation, as well as to manage complications from branch retinal vein occlusion and diabetic retinopathy [13, 14].

Research in both animals and infants has shown the involvement of inflammatory mediators in the development of ROP [15-19]. Dexamethasone eye drops are commonly used in preterm infants to reduce local inflammation after laser treatment for severe ROP. Öhnell et al., in a retrospective uncontrolled study, reported regression of severe ROP in infants following dexamethasone eye drops prior to planned laser treatment [20], and Yagi et al. observed comparable results in a pilot study [19]. If treatment with dexamethasone eye drops efficiently prevents the progression of ROP with less severe disease and fewer cases requiring treatment, infants may avoid general anaesthesia and retinal sequelae. However, no clinical trial has yet evaluated the efficacy and safety of administering dexamethasone eye drops to preterm infants with severe ROP. Topical administration of dexamethasone has been studied in a mouse model of ROP, oxygen-induced retinopathy (OIR), and when administered concurrently with oxygen exposure in OIR, a protective effect has been reported [17]. However, the timing of administration appears to be critical, as topical dexamethasone administered before the peak of neovascularization in OIR suppressed neovascularization by 30%, whereas later dexamethasone treatment had no effect [18]. In OIR, optimally timed topical dexamethasone administration and reduced neovascularization were associated with enhanced retinal mitochondrial function and decreased inflammatory response in immune cells [19]. Thus, research from OIR supports the clinically reported findings that topical dexamethasone may be an effective strategy to prevent severe ROP. Understanding the importance of timing in steroid treatment may explain previous conflicting results regarding intravenous and oral corticosteroids and ROP development [21, 22].

Studies on the efficacy and safety of dexamethasone eye drops to prevent severe ROP needing treatment in preterm infants are warranted. We designed a prospective, randomized, double-blinded, controlled, multi-centre intervention trial to include preterm infants with severe ROP not fulfilling treatment criteria, i.e. infants with Type 2 ROP and infants with stage 2 ROP in posterior zone II. We aim to reduce the number of infants with severe ROP needing treatment by 60% with the dexamethasone intervention compared to placebo.

Methods/design

Study design

The study is a national multi-centre, randomized, double-blinded, controlled prospective trial. The intervention group receives dexamethasone eye drops, 1 mg/ml (Dexafree[®]), while the control group receives placebo, saline (Drop-it[®]). The study consists of an intervention phase (main) study and an extension phase (follow-up) study. Figure 1 gives a schematic overview of the complete study schedule.

Professor Ann Hellström (ann.hellstrom@medfak. gu.se) is the primary sponsor and principal investigator (PI) in this study. The steering group is composed of three experienced paediatric ophthalmologists. The first infant was enrolled on 2022/09/22, and recruitment is ongoing.

Study population

The following centres in Sweden participated in the study: Sahlgrenska University Hospital (Gothenburg), Karolinska University Hospital (Stockholm), the university hospitals in Umeå, Uppsala, Örebro and Linköping. Södra Älvsborgs hospital, Skaraborgs hospital (Skövde), Ryhov hospital (Jönköping), and the hospitals in Karlstad, Växjö, Gävle, Östersund, Västerås and Eskilstuna.

Inclusion and exclusion criteria

Infants are eligible if they fulfil the following criteria:

- Infants born with a gestational age (GA) < 30 weeks.
- ROP stage 1 or stage 2 without plus disease in zone I.
- ROP stage 2 or stage 3 in posterior zone II without plus disease, with or without notch in zone I.
- ROP severity must be documented using wide-field digital imaging system photography (RetCam), and eligibility must be confirmed by at least two of three experienced paediatric ophthalmologists in the steering group.
- Signed informed consent by the parents/guardians (oral and written information).

The exclusion criteria are:

Ongoing ocular infection.



Fig. 1 Schematic overview of the complete study schedule

Table 1 Administration schedule for e	eye drops according	to ROP severity	in affected ey	/e/eyes
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	Number of drops per day
ROP stage 1–2 without plus disease in zone I	1 drop every other day
ROP stage 2 without plus disease in posterior Zone II	1 drop every other day
ROP stage 3 without plus disease in zone II, with or without notch in zone 1	1 drop daily
Type 1 ROP* fulfilling treatment criteria	If anti-VEGF injection is planned, eye drops should be immediately withdrawn
ROP treatment and post treatment	Routines at the clinic

Abbreviations: ROP Retinopathy of prematurity, VEGF Vascular endothelial growth factor

*Any stage of ROP in zone I, with plus disease; ROP stage 3 in zone I, without plus disease or ROP stage 2 or 3 in zone II, with plus disease

• If the neonatologist or ophthalmologist considers the infant unsuitable for the study.

Eligibility, randomization and blinding

Infants evaluated for eligibility for enrollment in the study will be identified at routine ROP screening by the local ophthalmologist. ROP evaluations will adhere to clinical screening practice according to national guidelines. RetCam will be used at the ROP screening to document the extent of ROP disease, and images will be saved in the clinical record file. When the ROP screening ophthalmologist evaluates eligibility, the PI and the steering group will be contacted. Images will be evaluated, and eligibility for inclusion must be confirmed by at least two of three ophthalmologists in the steering group.

Parents/guardians will be given oral and written information about the study via the HOPE Parent Application (Addi Medical) and asked to participate if the infant is eligible. The signed informed consent will be collected before any study-specific data is reported and the infant is randomized. Randomization will be performed stratified by centre by a study nurse using an electronic application (HOPE). After randomization, the study nurse will provide eye drops to the assigned neonatal nurse in the neonatal intensive care unit (NICU) for administration or to the parents or guardians if the infant is discharged from the hospital. In case of problems regarding the study eye drops, a randomization list is safely stored in a locker at the NICU and available 24 h/day in case of emergency and safety issues. All investigators, ophthalmologists, staff, and patients/guardians, except pharmacists, are blind to the participants' eye drop assignments. The single-dose containers for dexamethasone and placebo are similar, and identification of drop content will not be visible to an untrained eye.

Intervention

Study patients will be randomized to receive eyedrops with either dexamethasone 1 mg/ml (Dexafree[®]) in single-dose containers supplied by Thea Nordic or placebo, saline (Drop-it[®]) also in single-dose containers. Saline (Drop-it[®]) is a sterile, buffered saline without preservatives, with the same sodium chloride content as the tear film. The dose of dexamethasone has been adjusted to maintain efficacy while minimizing the medication dosage.

Based on the severity of ROP, the eye drops are administered at a dosage of one drop every other day to one drop daily in affected eyes, Table 1. The maximum intervention duration is 12 weeks. The dosage will be adjusted within the protocol's range if ROP regresses or progresses. When discontinuing intervention, drops are tapered over one week; if the infant receives one drop daily, the dosage should be reduced to one drop every other day for one week before discontinuing intervention. After laser treatment, the infant will receive dexamethasone 1 mg/ml to reduce post-laser inflammation; the dose and duration will be determined by the ophthalmologist in charge, based on local routines. If anti-VEGF treatment is planned, all eye drops will be stopped immediately to reduce the risk of infection and endophthalmitis in cases of dexamethasone intervention. To reduce systemic absorption of the medication, we inform caregivers to tilt the baby's head to the left when the left eye is given a drop and to the right when the right eye is being dropped and instantly wipe off the excessive fluid with a soft compress. Intervention will be given at several weeks of age and during a limited period.

The parents/guardians will record doses provided to the infant at home in the HOPE parent application. The total number of single doses used, along with compliance, will be estimated by collecting information about the number of doses returned and recorded in the HOPE application.

Subject withdrawal

The parents/guardians can withdraw the infant from the study at any time. Infants may be withdrawn from the study by the attending neonatologist or the PI for safety reasons, such as adverse events (AE) (clinical events or laboratory values), major protocol deviations, or significant deteriorations in the patient's condition that warrant discontinuation of the intervention. The final examination/sampling at study termination must then be performed at the time of the study discontinuation. Infants who withdraw from the study will not be replaced.

Primary outcome of the intervention study

The primary objective is to evaluate if dexamethasone eye drops, compared to placebo, reduce the proportion of infants with severe ROP from progressing to severe Type 1 ROP needing treatment.

Secondary outcomes of the intervention study and follow-up

The secondary objectives are to compare the following outcomes between the dexamethasone intervention and placebo:

- Time from detection of severe ROP to Type 1 ROP.
- Recurrences after laser/anti-VEGF treatment.
- Retinal morphology at 40 weeks postmenstrual age (PMA) and at 2 and 5.5 years of age.
- Change in intraocular pressure from before the intervention to 1–2 weeks after the intervention starts and at the end of the intervention.
- Visual acuity, refraction, orthoptic and ophthalmological status at 2 and 5.5 years of age.

Exploratory outcomes of the intervention study and follow-up

Leftover blood from clinical blood sampling will be studied regarding selected biomarkers and their relation to ROP development and intervention effect.

Safety outcomes in the intervention study

Clinically significant changes (abnormalities) from the physical examination of the infant or abnormal laboratory values will be recorded as an AE, starting from the time of randomization until the intervention phase termination visit. Ongoing AE at the intervention phase termination visit will be followed until the event is resolved or stable. Especially signs of increased ocular pressure (> 20 mmHg) or abnormal growth (> 1 standard deviation difference in weight, length and head circumference) after the start of intervention will be monitored as these are well-recognized side effects of high-dose steroid treatment, although this treatment is considered to be low dose. Other collected study-specific AEs will be pulmonary haemorrhage, pneumothorax, bronchopulmonary dysplasia (BPD), pulmonary hypertension, hypotension, circulatory instability, surgical patent ductus arteriosus (PDA), medical PDA, hypoglycemia, hyperglycemia, insulin treatment (glucose > 10 mmol/L at 2 independent time points), necrotising enterocolitis (NEC), perforated gut, ileus, enterostomy, sepsis, meningitis, intraventricular haemorrhage (IVH), and hydrocephalus. For each AE the following data will be recorded: AE diagnosis, AE start and end date, action taken regarding AE, AE outcome (resolved, ongoing, death, or lost to follow-up) and AE causality (not related, possibly related, related). Any severe AE (SAE), death or life-threatening event will be reported from the investigator at each site to the PI within 24 h of knowledge of the event. The local investigator and PI can stop the intervention temporarily or discontinue the infant from the study. If the infant is discontinued from the study, proper study termination procedures, including examinations and samplings, must be followed accordingly. The PI must report discontinuation due to an AE/SAE immediately to Thea Nordic.

Study procedures and data collection at intervention phase visits

All data are collected and stored in agreement with good clinical practice guidelines and in accordance with the General Data Protection Regulation.

Table 2 presents the study schedule for visits and procedures in the "intervention phase" (main) study and the "extension" (follow-up) study. The intervention phase study termination visit is planned to occur approximately at PMA 40 weeks or two weeks after the eye drop intervention ends, regardless of regression of ROP or ROP treatment.

The following data on infant and mother characteristics and medical history will be collected:

- Infant's birth characteristics: GA at birth, sex, birth weight (grams), birth length (cm), birth head circumference (cm), single/twin/triplet, age at inclusion in the study.
- Infant's medical history: lung morbidities like BPD, circulatory instability and PDA, gut problems like ileus and NEC, infections like sepsis, IVH and hydrocephalus. All surgical interventions.
- Mother's age (years) and mother's medical history: pregnancy complications, preeclampsia, infection requiring antibiotics, diabetes, hypertension or other disease requiring medication, parity, in vitro fertilization.

	Intervention phase (Main) study						Extension study		
Procedures	ROP screening Visit R0	Clinical visit Visit C1	ROP screening/ intervention		Clinical visit (40w PMA)	Termination visit ^b	Follow-up		
			Visit R1	Visit R2	Visit RX ^a	Visit C2	Visit T1	2 yrs Visit F1	5.5 yrs Visit F2
Data collection and stuc	ly procedures								
Informed consent	Х								
Eligibility	Х								
Medical history/charac- teristics of infant/mother	Х								
ROP evaluations	Х		Х	Х	Х				
RetCam photography	Х		Х	Х	Х				
Randomization		Х							
Dexamethasone/ placebo intervention dispense/return		Х	Х	Х	Х	Х	Х		
ROP treatment with laser and/or anti-VEGF			Xc	Xc	Xc				
Intraocular pressure	X ^d		Xd	Xd			X ^d		
MRI ^e + Peapod						Xe			
Physical examination		Х				Х		Х	Х
Weight, length, head circumference		Х	Х	Х	Х	Х		Х	Х
Vital signs: SpO2, heart rate, blood pressure		Х					Х		
Blood samples		Xf	Xf	Xf	Xf	X ^f	Xf		
Saliva cortisol		Х	Х	Х	Х		Х	Х	Х
Urine sample		Х				Х	Х		
Adverse events	Х	Х	Х	Х	Х	Х	Х		
Visual outcome and refractive errors								Х	Х
Retinal morphology with OCT								Х	Х
Diagnoses and compli- cations								Х	Х
Study termination		Х	Х	Х	Х	Х	Х	Х	Х

Table 2 DROPROP study schedule for study procedures and data collection

Study protocol version 4

Visit R0= Visit before start of intervention

Visit C1 = Clinical visit 1 (start of intervention)

Visit R1 = 1 week after start of intervention

Visit R2 = 2 weeks after start of intervention

Visit C2 = Clinical visit 2 (40 weeks PMA)

Visit T1 = 2 weeks after end of intervention

Abbreviations: OCT Coherence tomography, PMA Postmenstrual age, ROP Retinopathy of prematurity, SpO2 Oxygen saturation, VEGF Vascular endothelial growth factor

^a Visit RX = ROP Screening and intervention as many as required in order to be correctly followed-up regarding the monitoring and treatment of the ROP disease, procedures performed weekly

^b Main study termination visit occurs two weeks after the last intervention or at earliest at 40 weeks PMA when maximum ROP should have occurred

^c ROP treatment provided when required according to guidelines

^d Intraocular pressure will be measured before intervention, 1 and 2 weeks after start of intervention and after end of intervention

^e If performed in clinical routine, PeaPod in Gothenburg

^f If clinical sample is taken left over blood is collected for analyses

Intraocular pressure will be measured, and samples for salivary cortisol will be taken before intervention and thereafter according to the study protocol. Vital signs such as oxygen saturation (SpO2), heart rate and blood pressure will be measured before and after the intervention. At all clinical study visits, weight, length, and head circumference will be recorded. Body composition with PeaPod at 40 weeks PMA will be performed at sites where PeaPod is available. Brain Magnetic Resonance Imaging (MRI) will be performed at 40 weeks PMA according to clinical routine. Glucose in urine will be monitored after the initial start of intervention and at 40 weeks PMA. If intervention continues after 40 weeks PMA, a urine sample will be taken two weeks after the completion of intervention at the study termination visit. Leftover blood from clinical sampling will be analyzed for biomarkers involved in ROP-related processes such as angiogenesis, neurogenesis and inflammation (Gothenburg site).

Extension study

In an extension part of the study, an ophthalmological follow-up at 2 and 5.5 years of age will evaluate the child's best-corrected vision with an age-appropriate visual chart, refractive errors in cycloplegia, ocular motility, strabismus, nystagmus, and stereopsis. Retinal morphology with ocular coherence tomography (OCT) will be performed to evaluate the optic disc and maculae region. Neonatal and ophthalmological diagnoses and complications, as well as children's growth parameters, will be collected at follow-up.

Sample size

Natural history studies of ROP suggests that 50% of infants with ROP stage 2 in posterior zone II with haemorrhage or ROP stage 3 in zone II develop Type 1 ROP needing treatment [1]. We aim to reduce the number of infants progressing to severe ROP needing treatment with laser and/or anti-VEGF by 60%. Assuming 50% of infants need ROP treatment in the placebo group and 20% in the dexamethasone group, alpha 0.05, using a two-sided Fisher's exact test, would require 45 infants to be included per study group (1:1 ratio), in total, 90 infants excluding dropouts, to achieve a power of 80%. Taking into account a 10% drop-out rate, five infants per study group and thus 100 infants in total will need to be included.

Data monitoring

The data will be entered into a database, where internal review and programmed computer checks will be used to identify selected protocol violations and data errors. A statement will be obtained from each infant's parents/ guardians participating in the trial permitting the release of the infant's medical records as necessary for monitoring or inspection by authorized personnel for the PI and Regulatory Authorities.

Case report forms

The PI will be responsible for the database containing the information collected in the study retrieved from the eCase Report Forms (eCRFs). The eCRFs will be developed using the HOPE platform from ADDI Medical (www.addimedical.se).

Data monitoring committee

A Data Monitoring Committee (DMC) will be appointed, including an independent group of experts in the area that are not the Study PI or part of the study's steering committee, with one ophthalmologist, one neonatologist, and one epidemiologist, that will scrutinize the data prepared by a non-voting statistical programmer. Two planned closed DMC meetings will be held, the first when 35% of the infants have been followed until the main study ends, and the second when 70% of the infants have been followed until the main study ends. DMC will analyse data for efficacy (benefit) and safety (harm) at both time points. Ó'Brian-Flemming group sequential boundaries on the positive side will be applied for evaluation of potentially halting the trial because benefit has been shown, and a z-value exceeding 2.40 will be applied for evaluation of potentially halting the trial because harm has been shown. DMC may decide, given the descriptive data to not perform formal statistical interim tests if there is no sign of need for formal analyses for stopping for harm and stopping for efficacy. The DMC will not be responsible for stopping the study for futility. Given that the formal statistical interim tests are performed, the final *p*-values must be updated based on the number of interim tests performed. DMC may also, if necessary, schedule additional DMC meetings between planned closed meetings.

Information about study results will be strictly held within the closed DMC group. After a closed DMC meeting, the PI and the study's steering committee will only receive a recommendation to stop or continue the study.

Statistical analysis

All detailed statistical methods will be documented in a statistical analysis plan.

All analyses will be performed using either SAS software version 9.4 or later (SAS Institute Inc, Cary, NC, USA) or SPSS software version 26.0 or later (IBM Corp, Armonk, NY).

For tests between two groups, Fisher's exact test will be used for dichotomous variables, Mantel–Haenszel Chi-square trend test for ordered categorical variables, Chi-square test for non-ordered categorical variables and Fisher's nonparametric-permutation test for continuous variables. All efficacy evaluations will be adjusted for centre (strata in randomization) and gestational age (the most prominent risk factor). The difference between the two study arms with respect to binary outcomes such as the primary variable will be evaluated using logistic regression, for time-to-event data using Cox proportional hazards model, for number of recurrences per follow-up time using Poisson regression, for continuous outcomes using analysis of covariance (ANCOVA) or Fisher's non-parametric permutation in case of not normally distributed data, and continuous outcomes repeatedly measured over time using mixed models for repeated measures.

All tests will be two-tailed. The primary analysis will be considered confirmed if p < 0.05.

Ethical considerations

The protocol, informed consent form, and other written infant information have been submitted to the "Etikprövningsmyndigheten" (EPN, www.epn.se) in Sweden, (Ethical Dnr 2020–06028, Eudra-CT, 2020–004933 - 19 and CTIS, 2023–505318 - 97–00). The written unconditional approval was obtained prior to the study's commencement and was forwarded to Thea Nordic, the manufacturer of the study medication, prior to shipment of study medication supplies to the centre. The study protocol has undergone independent peer-review to gain funding from a major external funding body.

Discussion

This paper presents the DROPROP protocol: a prospective, randomized, multi-centre, double-blind trial designed to evaluate whether dexamethasone eye drops reduce the proportion of infants with severe ROP progressing to Type 1 ROP needing treatment compared to placebo. The findings of this study may impact the care of future preterm infants at risk of developing sight-threatening severe ROP worldwide.

As survival rates for preterm infants rise, the number of infants affected by sight-threatening ROP and needing ophthalmological expertise increases accordingly [2]. There is a concerning shortage of ophthalmologists available for ROP screening and treatment in many countries. We believe that dexamethasone eye drops could be a simple and low-cost treatment to reduce ophthalmological complications and lifelong visual impairment in these vulnerable new survivors. Research including preterm infants is challenging as they are particularly vulnerable and frequently experience critical illness and have uncertain prognoses [23]. Nevertheless, research is crucial, especially if it enhances our understanding or treatment of a medical condition [24]. Historically, clinical misadventures have occurred due to insufficient paediatric clinical research and off-label use of medications [25].

Research involving high-risk patients raises several ethical issues, particularly balancing potential risks and benefits. We acknowledge the safety concerns of topical dexamethasone intervention in our study. Intravenous or oral dexamethasone is commonly used in preterm care, i.e., to wean preterm infants from the ventilator and to prevent BPD. When used to prevent BPD, an initial high and then a tapering dose of 0.5 mg/kg per day of dexamethasone on the first day of life has been associated with an increased risk of cerebral palsy and impaired motor and cognitive development. However, treatment after one week of age and lower doses have not been shown to have the same adverse effects [21, 22]. The volume of a commercial eye drop is 50–75 μ l, and the concentration of dexamethasone in Dexafree® eye drops is 1 mg/ml. Accordingly, we expose the infant to only 0.1-0.15 mg/day. Common ocular side effects of shortterm topical dexamethasone are local discomfort during application and increased intraocular pressure, first noticed during the first two weeks of treatment (according to the product information of Dexafree[®]). We will, therefore, measure the intraocular pressure before and after one and two weeks of intervention and after ended intervention. Although systemic side effects are unlikely with the small doses of dexamethasone administered, we will closely monitor the infants' weight and head circumference development as well as glucose levels in blood and urine during the intervention period and at 40 weeks PMA, a time point at which MRI of the brain will also be performed. We also address the risk of suppressed adrenal function and reduced endogenous cortisol production during intervention. Therefore, we collect saliva samples for cortisol measurement before and after intervention, weekly during intervention, and follow-ups at 2 and 5.5 years of age. We consider the use of local eye drops with a low dose of dexamethasone for a limited period (one to 12 weeks) to pose less risk to the infant than general anesthesia, laser and/or anti-VEGF treatment. The benefits of reducing potential risks associated with general anesthesia and destructive laser treatment, as well as exposing infants to anti-VEGF with unknown systemic effects, are substantial. Multiple studies have shown that infants treated for ROP have the poorest visual and cognitive outcomes [26, 27]. It is also well known that infants treated for ROP with laser and/or anti-VEGF have a higher risk for blindness than not developing ROP needing treatment [28, 29]. Both general anaesthesia and anti-VEGF-treatment are suspected to affect brain development [12, 30], and laser treatment is a destructive treatment that damages the peripheral retina [11].

In conclusion, we conduct this study to evaluate the effectiveness and safety of dexamethasone eye drops as a preventative therapy for preterm infants with severe ROP. The findings from our study aim to support clinical practice and national guidelines to provide the best care for this particularly vulnerable group of infants worldwide. We believe that our research has the potential to significantly benefit children by reducing the risk for visual impairments, thereby improving their quality of life.

We plan to publish the results of this study in peerreviewed journals and present data at national and international conferences.

Abbreviations

AE	Adverse Event
BPD	Bronchopulmonary Dysplasia
CRF	Case Report Form
DMC	Data Monitoring Committee
GA	Gestational Age
IVH	Intraventricular haemorrhage
NEC	Necrotizing enterocolitis
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
PDA	Patent Ductus
PMA	Postmenstrual Age
ROP	Retinopathy of Prematurity
SAE	Serious Adverse Event
SpO2	Oxygen saturation

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12887-025-05673-x.

Supplementary Material 1.

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Authors' contributions

A.H. is the principal investigator of this study. A.H., A.P., I. H P., D.L., L.G., K.S., and L.E.H.S, conceived and designed the initial draft of the study protocol with contributions from P.L., M.P-L., A.K.N., H M.Ö., G.J. and U.S. All authors were involved in the preconsensus process of the protocol. A.P. is the study statistician. P.L. wrote the initial draft of this manuscript based on the study protocol. All authors revised the manuscript, made important contributions and approved the final version. All authors revised the manuscript, made important contributions and approved the final version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This manuscript represents the content of protocol version 4, October 2022. Ethical approval of this study was obtained by the Swedish Ethical Review Authority, Ethical initial application Dnr 2020–06028 approved 2021/02/23, amendment Dnr 2022–02641 - 02 approved 2022/06/06 and amendment Dnr 2023–03225 - 02 approved 2023/06/29.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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