BMJ Open

Clonidine as analgesia during retinopathy of prematurity screening in preterm infants (cloROP): protocol for a randomised controlled trial

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To cite: Carlsen Misic M, Eriksson M, Normann E, *et al*. Clonidine as analgesia during retinopathy of prematurity screening in preterm infants (cloROP): protocol for a randomised controlled trial. *BMJ Open* 2022;**12**:e064251. doi:10.1136/bmjopen-2022-064251

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-064251).

Received 26 April 2022
Accepted 15 September 2022

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ABSTRACT

Introduction Preterm infants are at risk of negative consequences from stress and pain at the same time as they often are in need of intensive care that includes painful interventions. One of the frequent painful procedures preterm infants undergo is eye examination screening to detect early signs of ROP (retinopathy of prematurity). These examinations are both stressful and painful, and despite a multitude of research studies, no conclusive pain-relieving treatment has been demonstrated. The main aim of this trial is to investigate the analgesic effect of clonidine during ROP eye examinations.

Methods and analysis The planned study is a multicentre randomised controlled trial with a crossover design. Infants will be recruited from two different neonatal intensive care units (NICUs) in Sweden. Infants born before gestation week 30 (and therefore eligible for ROP screening) and cared for in either of the NICUs will be eligible for inclusion in the study. The primary outcome will be Premature Infant Pain Profile–Revised score within 30 s after starting the examination. Secondary outcomes will be changes in the galvanic skin response parameters (area small peaks, area huge peaks, peaks per second and average rise time) within 30 s after starting the eye examination, together with the number and evaluation of adverse events reported within 72 hours after the examination and the examining physician's assessment of how easy the infant was to examine.

Ethics and dissemination Approval from the Swedish Ethical Review Authority and the Swedish Medical Products Agency has been obtained for the study. Parents of eligible infants will be getting both verbal and written information about the study including that participation is voluntary. Data will be collected and treated in accordance with the European general data protection regulations. The results will be reported on group level and published in a scientific journal.

Trial registration number ClinicalTrials.gov (NCT04902859).
EudraCT (2021-003005-21).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, this will be the first study investigating the pain-relieving effect of clonidine during retinopathy of prematurity (ROP) eye examinations of preterm infants.
⇒ The study will investigate the pain-relieving effect from both indirect ophthalmoscopy and RetCam, whereas the results from the two examination techniques/sites cannot be compared.
⇒ Recording facial expressions during eye examinations can be difficult but still gives us the opportunity to go back and review over again.
⇒ The crossover design with every infant as its own control will reduce many confounding factors.
⇒ Since there are no previous successful studies decreasing the pain from ROP eye examinations, the sample size calculation is built on findings from studies on other procedural pain.

INTRODUCTION

Preterm infants are sensitive to stimuli and are at risk of short-term and long-term negative consequences from stress and pain. They are often in need of intensive care that includes painful interventions. Repeated painful experiences during the neonatal period can result in future negative effects in pain response,[1] brain development,[2 3] cognitive functioning[4] and cortisol levels.[5] These infants are also at risk of secondary complications from their prematurity, one being retinopathy of prematurity (ROP). This condition is caused by abnormal blood vessel growth that can progress to retinal detachment and blindness. A low gestational age and low birth weight are risk factors for ROP,[6] and all infants born before gestation week 30 are therefore screened with regular eye examinations until the retina is fully developed.[7]

The eye examinations are painful and stressful for the preterm infant. The infant needs to be restrained during the examination, and bright light as well as physical manipulation of the eye with eye speculum are some of the aspects that can be painful and stressful.[8]

The mydriatic eye drops used before the examination also cause pain.[9]

Considerable amount of research has examined a variety of potentially pain-relieving interventions during ROP eye examinations without finding an effective treatment. Studies on oral sweet solutions that are effective as pain relief during other painful procedures have shown inconclusive results,[10–13] and a few that have shown significantly lower pain scores with sweet solutions are still showing pain scores within the limits for severe pain in the experiment group.[14 15] Non-pharmacological interventions such as skin-to-skin contact[16] and facilitated tucking[17] have also shown an inadequate pain relief as well as inhaled nitrous oxide.[18] A randomised controlled trial investigating morphine as pain relief during ROP screening had to be terminated due to adverse effects.[19] Despite multimodal techniques, the pain relief during ROP eye examinations seems to be insufficient,[20–23] leaving preterm infants exposed to repeated untreated pain.

Clonidine is an alpha-2 agonist that is used increasingly in neonatal care due to its safe sedating and pain-relieving properties,[24] without the risk of respiratory depression.[24 25] The use of clonidine can also reduce the need for other sedation and pain-relieving medications,[26] and some data also indicate neuroprotective capacities.[27]

Considering the pain and stress during ROP eye examinations and as of today the lack of effective pain relief methods, the aim of this study will be to investigate the pain-relieving effect of clonidine during ROP eye examinations.

METHODS AND ANALYSIS

Study design

This study is a multicentre randomised controlled trial with a crossover design. Infants will be recruited from two different neonatal intensive care units (NICUs) in university hospitals in the central part of Sweden (NICU A and NICU B). Infants born before gestation week 30 (and therefore undergoing ROP screening) and cared for in either of the NICUs will be eligible for inclusion in the study. Previous studies on ROP screening-induced pain revealed a mean Premature Infant Pain Profile (PIPP) score of 10.3 (SD 4.2)[16] and 16.4 (1.8)[14] in the control groups. Based on the literature,[28] a difference of two steps in the primary outcome variable PIPP-Revised (PIPP–R) could discriminate between painful and non-painful situation, and thus is considered clinically significant in this study.

With a power of 0.8 and a significance level of 0.05, 18 infants are needed to detect this difference and with consideration of potential dropouts, the aim is to include 25 infants. Because of different examination techniques at the respective units, we plan to include 25 infants at each unit. In unit A, RetCam (Clarity Medical Systems, Pleasanton, California, USA) is used for ROP screening, while direct ophthalmoscopy is used almost exclusively at unit B.

Exclusion criteria

- Infants who have received pain-relieving analgetics, sedatives or beta-blockers within 24 hours before the eye examination.
- Previous documented renal failure.
- Infants without gastric tube.
- Infants with known heart arrhythmias or neurological deficit.
- Infants with circulatory instability (assessed as a mean arterial blood pressure below infants' gestation age in weeks).

The study will be monitored by an independent monitor appointed by the physician responsible for the study (MP). Monitoring will be performed according to risk- based monitoring and a monitoring plan.

Procedure

Parents of eligible infants will receive written and verbal information about the study before the first scheduled eye examination. The principal investigator on each site will obtain informed consent from the parents. The infant will serve as his or her own control and will be examined according to the units' policy. After parental consent, the infant's first two eye examinations will be included in the study. To minimise potential effects from previous experience, the order of the treatment (clonidine or placebo) will be randomised for each infant using an online random sequence generator that gives the order. The allocation for the treatments will be kept in opaque envelopes and an unblinded trained nurse or pharmacist, not involved in the study, will prepare the study solution (clonidine or sterile water) in a syringe marked with the patient's study ID. Both clonidine and sterile water will be retrieved from the units' ordinary medical supply. A document with the included patients' allocations will be kept in a closed envelope inside a locked room in the respective NICUs in order to make unblinding possible if needed.

Sixty minutes before the first eye examination, the infant will receive clonidine 4 µg/kg (intervention) or sterile water (placebo) in equivalent volumes in the nasogastric tube by a nurse blinded for the content. Everyone else in the room will be blinded for the content of the syringe as well as the researcher performing the subsequent analyses. Mydriatic eye drops (cyclopentolate 0.5% and phenylephrine 0.5%) will be administered according to clinical routine at 45 and 30 min before the procedure. The infant will be connected to a probe measuring oxygen saturation and heart rate on one foot and three electrodes measuring GSR (galvanic skin response) on the other foot before the procedure. The ophthalmologist will then examine the eyes with either RetCam or direct ophthalmoscopy according to the respective units' guidelines. In addition to the study solution, the infant will receive standard care with facilitated tucking and a pacifier. The infants' face, expressions, heart rate and oxygen saturation values from the monitor display will be video recorded by two cameras before, during and

Table 1 Overview of outcomes

Primary outcome	Secondary outcomes
Premature Infant Pain Profile–Revised score within 30 s after starting the eye examination.	Changes in galvanic skin response parameters within 30 s after starting the eye examination.
	The number, and evaluation, of: ► Adverse events ► Serious adverse events ► Sudden unexpected serious adverse reactions reported within 72 hours after the examination will be measured.
	The examining physician's assessment of how 'easy' the infant was to examine.

after the examination for subsequent PIPP-R assessments. From these video recordings, one researcher will perform the PIPP-R pain assessments including noting the baseline values as well as the values within 30 s after the beginning of the eye examination according to the instructions of the PIPP-R scale.[28] The research group has previous experience of video recording and assessing pain with PIPP-R during eye examinations.[10] Afterwards, the examining ophthalmologist will estimate how easy the infant was to examine by marking an 'X' on a 10 cm-long horizontal line where one end indicates 'very easy to examine' and the other end 'very difficult to examine'. Though this is not a validated measure for examining difficulties, it will give an indication if clonidine or placebo affects the examining procedure. The ophthalmologist can also write any other comments in free text in the same document. The same procedure will then be executed during the infants' second eye examination with the study solution (intervention or placebo) he or she did not receive the first time.

Primary outcome

The primary outcome is the PIPP-R[28] score within 30 s after starting the eye examination (see table 1).

PIPP-R is a pain assessment scale for procedural pain consisting of three behavioural parameters (brow bulge, eye squeeze and nasolabial furrow), two physiological parameters (oxygen saturation and heart rate) and two contextual parameters (gestational age and behavioural state). An assessment will result in a score between 0 and 21 where a higher score indicates a higher level of pain. A Swedish version of the scale will be used in the study.[29] The PIPP-R assessments will be performed by one of the researchers (MCM), and 20% of them will also be assessed by another researcher with extensive experience in pain assessment (EO) in order to assess inter-rater reliability.

Secondary outcomes

The secondary outcomes are changes in the GSR parameters (area small peaks, area huge peaks, peaks per second and average rise time) within 30 s after starting the eye examination. GSR is recorded with the Pain Monitor (MedStorm, Oslo, Norway) and reflects changes in activity in the sweat glands in response to sensory stimuli such as pain.[30]

The number and evaluation of adverse events (AEs), serious AEs (SAEs) and sudden unexpected serious adverse reactions (SUSARs) reported within 72 hours after the examination will also be measured as secondary outcomes as well as the examining physician's assessment of how easy the infant was to examine. Any AEs, SAEs and SUSARs will be recorded in the patients' case report form (CRF) in accordance with regulations from the Swedish Medical Products Agency.

Demographic and medical data about the infant such as gestational age, birth weight, apgar, current weight and time since last feeding will also be recorded.

Data analysis

The data from the respective units will be analysed independently for each unit. The primary outcome (PIPP-R) will be analysed and reported with the Mann-Whitney U test. The secondary outcomes (VAS (visual analogue scale), GSR) will be analysed and reported with parametric statistics (mean, SD, paired t-test) when the data are normally distributed and non-parametric statistics (median, IQR and Mann-Whitney U test) when not normally distributed. Level of significance is set to 0.05.

The population will be all randomised patients according to intention to treat. Dropouts and missing data will be reported in the final report.

Patient and public involvement

There will be no patient or public involvement in this study.

ETHICS AND DISSEMINATION

The study is registered in the ClinicalTrials.gov Database (NCT04902859) and European Union Drug Regulating Authorities Clinical Trials Database (EudraCT 2021-003005-21).

The study protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials guidelines and checklist.[31] Approval from the Swedish Ethical Review Authority (2021-03610) and the Swedish Medical Products Agency (2021-91712) has been obtained for the study. Parents of eligible infants will receive both verbal and written information about the study including that participation is voluntary. Data will be collected and treated in accordance with the European data protection regulations. To protect the identity of the individual patients, all data will be registered with a unique code. The key for the code will be stored in a safe place where no unauthorised persons will have access.

Individual, coded data will be collected and registered in a CRF that will only be accessible for the researchers involved in the project. The recorded videos on the

infants' faces and saturation/heart rate values as well as GSR values will be collected, registered with the same code and stored on a safe database for the study. Data will be stored for a minimum of 10 years after the completion of the study. Results from the study will be published in a scientific journal and reported on group level.

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Contributors All authors (MCM, ME, EN, MP, YB and EO) have planned and designed the study. EO wrote the first draft of the manuscript, and MCM, ME, EN, MP and YB critically appraised and revised it.

Funding This work was supported by the Research Committee at Region Örebro county (grant number: OLL-934822) and Lilla Barnets Fond (grant number: YE1353).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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