2019

Little Eye Drop Study

Study Protocol for the Randomised Controlled Non-Inferiority Trial: Microdrop Administration of Phenylephrine and Cyclopentolate Eye Drops in Neonates

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1.0 Introduction

1.1 Background

Key messages

1. Very premature infants need to have retinopathy of prematurity eye examinations to help prevent permanent blindness
2. Some neonatal units in New Zealand and Australia are using doses of mydriatic eye drops that exceed an adult dose
3. Pilot data suggests that low dose eye drop regimens are effective at sufficiently dilating the pupil
4. Microdrop administration of mydriatic eye drops has not been well studied
5. The safety of mydriatic eye drops is not well understood in the literature

Figure 1 Dr Mary-Jane Sime performing a retinopathy of prematurity examination

Retinopathy of prematurity (ROP) is a major cause of blindness in children who were born before 31 weeks gestational age or with a birth weight less than 1250 g. Because of the risk of permanent blindness, this cohort of premature infants have routine ROP eye examinations (ROPEE). With early detection of retinopathy, timely interventions can be given to treat this condition.

The eye examination involves a two-step process; 1) administration of mydriatic (pupil dilating) eye drops, and 2) the eye examination. The eye drops are administered approximately 30 to 60 minutes prior to the ROPEE, and the eye exam occurs fortnightly, however if there are signs of retinopathy, the infant is likely to need weekly eye checks.

Sufficient pupil dilation is needed to obtain an adequate view of the retina, and to evaluate the health of the retina. Detecting early signs of ROP allows for timely treatment, therefore ensuring the infant has the best possible chance of preventing irreversible blindness and the lifetime of consequences of that for the child and their family.

Phenylephrine with cyclopentolate or tropicamide are the eye drop regimens that are used to dilate the pupil. We know from our recent survey of neonatal facilities in Australia and New Zealand, that there is a wide variety of these regimens in use. Regimens varied in concentration, drop volume and frequency of administration, and within this variation, 5 of the 11 centres were using adult doses, 2 were using more than an adult dose, and only 4 were using less than adult doses. Following administration, it is estimated that 80% of the eye drop volume enters the nasolacrimal duct and gains entry into the systemic circulation via the nasal mucosa.[1] Systemic absorption of mydriatics has been associated with clinically significant cardiovascular, respiratory, and gastrointestinal

adverse effects.[2] Therefore, guidance on clinical practice is required to help reduce the exposure of excessive doses that some premature infants are receiving.

Results from a systematic review of the literature suggested that low dose mydriatics are effective at sufficiently dilating the neonatal pupil for ROPEEs.[2] Data from our own pilot study indicate that microdrop administration of these medicines is another method to reduce the risk of systemic absorption, however only two Neonatal Intensive Care Units in New Zealand are using low dose microdrops.

1.2 Work to Date

The Dunedin based research group completed a pilot study in January 2019. The pilot study's primary objective was to investigate if phenylephrine 1% or 0.5% and cyclopentolate 0.2% or 0.1% in a microdrop volume would achieve adequate pupil dilation for retinal examination in premature neonates.

The secondary objectives were to describe the time-course of physiological markers of systemic absorption following eye drop administration (blood pressure, heart rate, feed intolerance), to determine if eye pigmentation (light or dark) is a significant covariate for phenylephrine and cyclopentolate induced pupil dilation, and to develop an eye colour chart to determine light iris vs dark iris.

Preliminary analysis on efficacy data suggests that a single microdrop administration of phenylephrine 1% and cyclopentolate 0.2% sufficiently dilates the neonatal pupil for the Ophthalmologist to carry out the ROPEE. All premature infants, irrespective of randomisation, had a successful ROPEE.

Preliminary analysis on safety data suggests that heart rate, blood pressure, and feed intolerance was not significantly different, clinically or statistically, between the two groups.

Data from the pilot study is currently being analysed in preparation for publication.

1.3 Multicenter Study

Although the results from the pilot study are encouraging, a larger RCT is required to substantiate the pilot data. To date, there is no large published dataset for the minimum mydriatic eye drop concentration that can be used to obtain sufficient pupillary dilation, nor information regarding the systemic safety of such a regimen. The proposed study will make a significant contribution to the published literature, and therefore, be available to guide safe and effective use of mydriatics for ROPEE.

Data from the pilot study has informed the design of the non-inferiority study for this multicentre RCT. A non-inferiority study design was chosen because it is anticipated that there will not be a statistically significant difference in terms of efficacy between the two mydriatic regimens, although medication-associated side effects may be reduced. Data collection for both efficacy and safety will be carried out (see 2.4 Outcomes further details).

This trial's Universal Trial Number is U1111-1233-2494, and is registered with the Australian New Zealand Clinical Trials Registry number ACTRN12619000795190p.

This trials Health and Disability Ethics Committee approval reference number is 19/STH/114 and was issued on the 20th June 2019.

2.0 Methodology

Masked randomised controlled non-inferiority trial. Per protocol study design (only those adherent to the treatment are included).

2.1 Participants

Participant demographic information that will be recorded: gender, ethnicity (according to neonates whānau/parent(s)/caregiver(s)), dark or light iris colour (potential confounder for pupil dilation), gestational age at birth and time of examination, birth weight and weight at time of examination, level of respiratory support (if any) and grade of retinal vascularisation and, or, evidence of retinopathy of prematurity, feed volume and type (e.g. breast milk, formula), past medical history (i.e. major complications, Apgar scores, mode of delivery), current medical condition(s), current medication(s).

Eligibility criteria

Neonates admitted to Invercargill, Dunedin, Christchurch or Wellington hospital's neonatal intensive care units, who are undergoing routine ROPEE in accordance with the National Guidelines.

Exclusion criteria

Neonates with, a) ROP greater than stage 2, b) current eye infection, c) not able to use phenylephrine or cyclopentolate eye drops.

2.2 Intervention

Participants will be randomised to receive either a combination of;

1. Reference treatment: one combination microdrop of both phenylephrine 1% and cyclopentolate 0.2% to both eyes, or
2. Low dose treatment: one combination microdrop of both phenylephrine 0.5% and cyclopentolate 0.1% to both eyes.

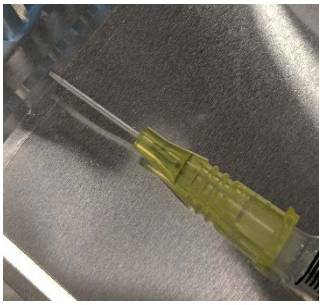

Figure 2 Microdrop: 24 gauge cannula (with needle removed)

The reference treatment has proven efficacy as shown by our pilot study data, and is the regular eye drop regimen that is used at Dunedin and Invercargill Hospital for neonatal ROPEE. The other low-dose regimen is being tested for non-inferiority.

If the pupil is insufficiently dilated with one drop, two further administrations can occur, 20 minutes apart.

A microdrop will be given by attaching a 24 gauge cannula (with needle removed) to the end of the syringe.

Eye drops will be compounded, labelled, product randomisation coding and delivered by Optimus Healthcare, Auckland.

2.3 Objectives

The hypothesis concerning non-inferiority is that there will not be a statistically significant difference between the two mydriatic regimens with respect to the Primary outcome.

Primary Objective

- To identify if phenylephrine 0.5% and cyclopentolate 0.1% in a microdrop volume is non-inferior to phenylephrine 1% and cyclopentolate 0.2%, by achieving adequate pupil dilation for a successful ROPEE in premature neonates.

Secondary Objectives

- To identify whether systemic absorption following eye drop administration has an unwanted effect on blood pressure, heart rate, feed intolerance and respiratory function.
- To determine if eye pigmentation (light or dark) is a significant covariate for phenylephrine and cyclopentolate induced pupil dilation.

Exploratory Objectives

- Rate of adverse drug reaction.

2.4 Outcomes

Primary efficacy outcome measurement

The research staff or nurse caring for the infant at the time of the ROPEE will verbally survey the ophthalmologist immediately after the ROPEE to ascertain the success of ROPEE/ease of ROPEE for the Ophthalmologist (easy vs difficult).

- Easy: fundal examination is not impeded by inadequate pupil dilatation.
- Difficult: fundal examination is impeded by inadequate pupil dilatation and either further mydriatic drops required to see the peripheral retina or additional manipulation required to overcome inadequate pupil dilatation.

Secondary efficacy outcome measurement

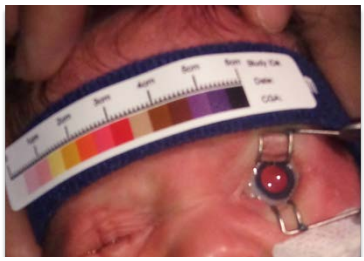

Figure 3 Red reflex and the Metric Graduated Colour Tool

Research staff will take a photo of both eyes at the time of ROPEE (approx. 30 - 45 min after eye drop instillation). The Metric Graduated Colour Tool (patent 2017904788), with NHI and participant number, will be placed on a CPAP chin strap and then attached to the infants forehead before a red reflex photo of both eyes (one at a time) will be taken with a digital camera. Each participant will be allocated a unique study participant number which will be written on the Metric Graduated Colour Tool prior to the photos being taken. The photos will then immediately be uploaded into DropBox, in the study participants folder. The case report form data will be uploaded into DropBox which will have both the study participants NHI and study number. Lisa Kremer will then carry out monthly preliminary analysis.

Photos of both eyes will be imported into the GIMP 2.8.20 image manipulation programme, where the Measure Tool will be used to measure the pupil diameter and compare to the Metric Graduated Colour tool. Pupil diameter measurement will occur prior to un-masking of randomisation.

Secondary physiological outcome measurements

Baseline blood pressure and heart rate measurements will be recorded. Subsequent measurements will be taken 20 min after eye drop instillation and then immediately before ROPEE. Phillips monitor will be used to take a manual blood pressure, preferably from the left upper limb. Three blood

pressure measurements will be taken, preferably when the infant is settled, and the measurement that is closest to resting state will be used.

Medical notes will be reviewed by a member of the research team or nurse caring for the infant, for any change in overall daily level of respiratory support for 24 hours prior, day of and day after ROPEE to identify any changes in support, e.g. changes in level of PEEP, change in mode of support, or persistent change in oxygen requirement.

Feed intolerance will be reviewed by retrospectively reviewing feed volumes and spills, on the observation chart, for 24 hours prior and 24 hours post eye drop installation. Medical notes will be reviewed retrospectively for any documentation of Necrotising Enterocolitis (NEC) for 7 days post mydriatic eye drop installation. NEC will be diagnosed according to Bells Criteria.[3]

In addition to the usual in-house adverse effect reporting form, and Center for Adverse Reaction and Monitoring form, any associated or causative treatment emergent adverse events (TEAE) will be recorded on the Case Report Form. Research staff or nurse caring for the infant will record serious treatment related TEAE, e.g. serious gastrointestinal symptoms, serious respiratory symptoms, or treatment related AE, e.g. prolonged crying, vomiting. It is not anticipated for there to be any TEAE to occur during the study period, however plans are in place should such event occur.

If any participant was injured in this study, which is unlikely, it is possible for the parents/whānau to apply for compensation from ACC. If any of the participants have private health or life insurance, the parents/whānau will need to check with the insurer that taking part in this study won't affect their cover.

2.5 Sample size

A total of 150 participants are required for the RCT, which equals 75 participants per group, with an estimated drop our rate of 3 per group. There will only be one set of data collected from each participant, and infants can be recruited from any ROPEE (could be their first ROPEE, 2nd, 3rd, etc).

Non-inferiority criterion that were considered when calculating the sample size are;

Sample size calculation completed by Associate Professor David Reith, who has completed a Masters in biostatistics and epidemiology, and went on to complete a PhD in mixed effects modelling.

a) Stata sample size calculation based on alpha 0.05 (one sided), power 0.8, p1 0.8, p2 0.95, n2/n1 1.
b) Based on Ophthalmology consultation, an acceptable mydriasis failure rate for improved safety is 15%.
c) There is a 5% probability of type 1 error with a normal distribution, therefore the *Z* value (two-sided) related to the probability of falsely rejecting a true null hypothesis (α) = 0.05 Z_α= 1.65 (one-sided). The *Z* value related to the probability of failing to reject a false null hypothesis (β) = 0.80 Z_β= 0.84.
d) Rigorous analysis of literature via a systematic review, identified that the neonatal pupil needs to be dilated by approximately 5mm or more, for a successful ROPEE.[2] Therefore the size of the effect that is clinically worthwhile to detect is approximately 5 mm.
e) Based on our pilot study, the drop out rate is likely to be close to zero.

2.6 Randomisation

a) Sequence generation: block randomisation will occur by computerised central randomisation.
b) Allocation concealment: allocation will remain concealed until analysis or in the event of an serious adverse event which requires seeing the dose that was administered to the participant.
c) Implementation: allocation sequence is to be generated by Lead Investigator. Consent will be obtained from whānau/cargiver by the NICU Research Nurse or by any other trained NICU staff member (e.g. Neonatal nurse, Paediatrician or Neonatologist).
d) Masking: whānau/caregivers, nursing staff administering the eye drops, staff assessing the outcomes (e.g. ophthalmologist, research nurse, PhD student) will be masked to the group assignment.

2.7 Statistical methods

Will be carried out by David Reith (Lead Investigator), and Lisa Kremer (PhD candidate).

The primary efficacy outcome measures are nominal variables, and the data set is less than 1,000, therefore the Fisher's exact test of independence will be used. The null hypothesis is that the relative proportions of the reference treatment are independent of group B.

The secondary efficacy outcome measures and secondary safety outcome measures include one measurement variable and one nominal variable, therefore a paired Student's t-test will be used. It is assumed that both groups will be normally distributed and homoscedasticity. The null hypothesis is that the means of the measurement variable are equal for the two groups.

An assumption is made that any missing data is missing completely at random. Missing data will not be imputed. Data will remain missing and will be reported.

2.8 Test

Data from test will be recorded on a case report form and will be de-identified.

A successful ROP screen, and therefore sufficient pupil dilation, will be deemed by the visiting Ophthalmologist.

2.9 Consultation with Māori

Consultation with the Ngāi Tahu Research Committee within the University of Otago and with Hine Forsyth (Te Rununga o Ngāi Tahu, Ōtākou Marae, iwi representative) will take place. Research Advisory Group-Maori will be consulted in Wellington and their approval sought.

2.10 Dissemination of Findings

- Whānau, parent(s) or caregiver(s) will be offered to be sent findings from the trial.
- Findings will be sent to the Research Manager, The Office of Māori Development, University of Otago, as recommended by the Ngāi Tahu Research Committee.
- Findings will be sent to Hine Forsyth, to be distributed to Ngāi Tahu if any information is found that is of relevance to Māori.
- Findings will be sent to the Christchurch Research Advisory Group Māori.
- Findings will be sent to the Wellington Research Advisory Group Māori.
- Findings, if accepted, will be published in neonatal/paediatric relevant journals.
- Findings, if accepted, will be presented at neonatal/paediatric relevant conferences.

References

1. Shell JW. Pharmacokinetics of topically applied ophthalmic drugs. *Surv Ophthalmol* 1982;26(4):207-18. doi: 10.1016/0039-6257(82)90081-9
2. Kremer LJ, Reith DM, Medlicott N, Broadbent R. Systematic review of mydriatics used for screening of retinopathy in premature infants. *BMJ Paediatrics Open* 2019;3(1):e000448. doi: 10.1136/bmjpo-2019-000448
3. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal Necrotizing Enterocolitis: Therapeutic Decisions Based upon Clinical Staging. *Ann Surg* 1978;187(1):1-7.