

**The Effect of Eyemasks on Neonatal Stress Following Dilated Retinal Examination, a  
Randomised Clinical Trial**

**(MASK-ROP)**

**Research Protocol and Statistical Analysis Plan**

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## **Introduction**

Retinopathy of Prematurity (ROP) is a disorder of retinal vascular development of the low birthweight preterm infant that may lead to blindness if untreated (1). The long term visual acuity of infants with ROP detected by screening examination can be improved by peripheral retinal ablation therapy or injection of anti-VEGF agents (2,3).

The screening examination for retinopathy of prematurity involves dilation with mydriatic eye drops, insertion of a lid speculum to retract the eyelids, and depression of the sclera to visualize the retina. These exams are routinely performed in Neonatal Intensive Care Units (NICUs) to facilitate early detection of ROP and guide treatment to prevent retinal detachment and blindness (3). However, infants undergoing this examination have shown elevations in heart rate, blood pressure, and desaturations at the time of the examination, and in the hours following (4). The frequency of apneic events experienced by these infants is increased in the 24-48 hour period after an examination (5).

Several studies have looked at the pain response to mydriatic drops and speculum insertion (6,7,8) as well as the systemic effects of the mydriatic drops. However, the cause of apneic events in the later post-examination period is unknown (5). We postulate that photosensitivity related to mydriasis is distressing for infants in the period before and after the ROP exam, potentially contributing to stressful events, including apnea(9).

We propose to test this hypothesis by applying a mask to cover the eyes of the infant after the instillation of mydriatic drops, leaving the mask on for 4 hours, the typical duration of mydriasis following a drop of cyclopentolate (10). We expect that this intervention will result in a significant reduction in the number of stressful events following an examination, and may reduce the amount of distress experienced by infants.(9)

## **Methods**

A dual-centre, prospective parallel group trial with balanced randomization (1:1) will be conducted. Infants requiring ROP screening will be automatically identified as part of routine hospital protocols. Participants will be recruited from the NICUs at St. Michael's Hospital and

Sunnybrook Health Sciences Hospital in Toronto, Ontario, Canada. Parents or caregivers of eligible infants will be approached and consented for participation in this study.

*Inclusion criteria:* Infant with birthweight of  $\leq 1500$  g or less or a gestational age of  $\leq 32$  weeks with no prior ROP screening. Examinations will be performed starting at either 4 weeks chronological age or 31 weeks post menstrual age, whichever is later.

*Exclusion criteria:* Pre-existing corneal abrasion/ulcers, ocular malformations that prevent dilation, and known neurological abnormalities that could affect response to pain. Not anticipating transfer to another institution were approached for participation. No prior ROP screening

A computer generated block randomization schedule will be made by the primary investigators, with a block size of 50 for each site (<https://www.randomizer.org/>). Assistants enrolling infants will be blinded to the randomization schedule and infants placed in the schedule in chronological order by date that consent was obtained.

*Protocol for Eye Examination:*

Cyclopentolate 0.5% and Phenylephrine 2.5% drops are to be instilled in both eyes to achieve mydriasis. After approximately 30 minutes, topical anaesthetic drops are instilled and a Barraquer wire speculum is used to retract the eyelids. Sucrose is given to soothe the infant prior and during examination. Indirect ophthalmoscopy with scleral depression is then performed to visualize the retina.

Infants in the treatment arm will have a standard phototherapy mask (Biliband, Natus, Pleasanton, California, USA) applied over the eyes after instillation of mydriatic drops. The masks will be removed 4 hours after the eye examination, when the pharmacologic effect of the mydriatic agents would have subsided. The mask will be removed for the examination but reapplied promptly afterward. Infants in the control arm received standard examinations with no masking.

Neonates are continuously monitored in both NICUs according to the standard of care. Apneic events, desaturation and bradycardic events are recorded based on nursing observation of monitor alarms and clinical status of the infant at the time of the event. An apneic episode is

defined as a cessation of respiratory effort >20 seconds, or less if accompanied by bradycardia, cyanosis or pallor. Low heart rate alarms were set at <100bpm; low pulse oximetry alarms were at <88%. Heart rate, blood pressure, oxygen saturation and distressful/apneic events were recorded hourly and retrospectively assessed for up to 48 hours after the instillation of eye drops.

Both NICUs employ variable lighting schemes, with lights turned down after ROP screening according to standard protocol.

### *Outcomes*

The primary outcome will be the total count of desaturations, bradycardic events, and apneic events (all “stressful events”) occurring 12 hours after examination in the treatment group compared to control, adjusted by the baseline rate of stressful events 12 hours before examination. Desaturations are defined as episodes when oxygen saturation falls below 88%, measured by pulse oximetry. Bradycardia is defined as a heart rate less than 100 beats per minute. Apneic events are defined as a pause in breathing for at least 20 seconds.

Secondary outcomes include

1. A sub-analysis of the effect of masking on reducing either desaturations, bradycardic events or apneic events.
2. Monitoring changes in heart rate, respiratory rate, and oxygen saturation in the 4 hours period after examination in both groups.
3. An exploratory analysis of baseline variables affecting the number of spells 12 hours after examination, including birth weight, age at examination, gestational age, ventilation needed during examination, ROP stage, medical co-morbidities, and medications.

### *Data Collection*

Data will be entered into each patient’s medical record as per standard of care by NICU nursing staff. All data collection and chart review will be done at each respective NICU >48 hours after ROP screening was performed, with data collectors blinded to treatment group.

### *Sample Size*

Mitchell et al. (5) showed an incidence of apnea of 9/23 (23%) in the first 24 hours after eye examination. Scenarios to compare the incidence between masked and control groups, given 80% power and alpha of 0.05 predicted a need of n=169 to detect a 50% reduction in apnea. As our primary outcome was all stressful events, which occur more frequently than apnea, an analysis of outcomes at n=50 was planned as this initial pilot study.

### **Statistical Analysis**

Descriptive statistics will be used to characterize patients at baseline and over time. We anticipate a low number of stressful events in each group as our primary outcome. Therefore, we plan to compare groups using a negative binomial regression model, adjusting for the total number of stressful events during the 12 hours pre-examination. Secondary analyses using negative binomial regression models will also be performed to assess differences between groups in desaturations and bradycardic events, and to examine the additional effect of baseline variables (i.e., including birth weight, age at examination, gestational age, ventilation needed during examination, ROP stage, medical co-morbidities, and medications) on the primary outcome, adjusting for total number of stressful events during the 12 hours pre-examination.

Linear mixed models for repeated measures will be performed for heart rate and respiratory rate, including time, group and the interaction of time by group, and assuming compound symmetry covariance structure. Apneic events will be compared between the groups with a Fisher's exact test.

Non-parametric Wilcoxon rank sum test will be used to measure changes in Oxygen saturation at different time points. All statistical analyses will be conducted using SAS (version 9.4, Cary, NC, USA).

### **Predicted Results and Potential Impact of Research**

We predict that infants that have had their eyes shielded from environmental light while dilated are less likely to experience distressful events in the 12 hour period following ROP screening. If this study shows decreased rates of distress using this therapy, it would be a very simple addition to current practice and be of benefit for premature infants undergoing an uncomfortable exam.

## References

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