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## Physiologic Effects of Retinopathy of Prematurity Screening Examinations

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### Abstract

**Purpose**—Preterm infants weighing <1500 grams routinely undergo a series of eye examinations to screen for retinopathy of prematurity (ROP). While these examinations are important for the prevention of blindness, infants may suffer adverse physiologic events during and after the examination. The procedure includes administration of mydriatic eye drops that may be absorbed systemically and physical manipulation of the eye that is accompanied by stress and pain. The purpose of the study was to monitor changes in infant health status and adverse physiologic events in the two days following ROP eye screening.

**Subjects**—The study used 50 preterm infants with a mean gestational age of 32 weeks, undergoing their first ROP examination in a NICU located in a university medical center.

**Design**—This pilot study used a prospective, descriptive design.

**Methods**—Physiologic changes and illness events were recorded before and for two days after the eye examination, using tools that tracked parameters of respiratory, cardiovascular, gastrointestinal, and neurological status. Data were collected directly from daily audits of medical records. McNemar's test for comparing paired proportions and the signed rank test were used for comparing significance of physiologic changes before and after the ROP eye examination.

**Principal results**—Apnea events increased significantly ( $p=0.04$ ) in the 24–48 hour period after the eye examination compared to apnea events before the eye examination. These results were based on 39 infants who were not receiving ventilator support. There was a significant difference in the frequency of oxygen desaturation events between infants with and without apnea (0–24 hours after examination  $p<0.002$ , 25–48 hours after examination,  $p<0.001$ ). There were no significant differences in heart rate, cyanosis, gastric residuals, or seizures after the eye examinations.

**Conclusions**—ROP examinations may be associated with increased apnea, a clinically significant problem. Nursing implications include careful monitoring of infants during and after

ROP eye examinations, discharge teaching for caregivers, and continued research on nursing interventions to prevent adverse physiologic events.

### Keywords

preterm infant; retinopathy of prematurity; screening examinations; apnea

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### Introduction

Eye examinations to screen for retinopathy of prematurity (ROP) are performed routinely in neonatal intensive care units (NICUs). These examinations are important because early detection and treatment of ROP can prevent detachment of the retina and resulting blindness. The American Academy of Pediatrics, American Academy of Ophthalmology, and American Association for Pediatric Ophthalmology and Strabismus<sup>1</sup> have issued a joint statement on the importance of routine ROP examinations for preterm infants with a birth weight less than 1500 grams or a gestational age of 30 weeks or less. Examinations are also recommended for neonates with current instability or a history of clinical instability who weigh between 1500 and 2000 grams. Table 1 presents recommendations for timing of the initial ROP eye examination. Infants are examined every 1 to 3 weeks, depending on progression of the disease, and treatment is provided as indicated. Table 2 outlines the unit protocol for ROP eye examinations.

Although ROP examinations are an important part of monitoring for the preterm infant,<sup>2</sup> these examinations are not without complications. There are many verbal reports from nurses working in NICUs of infants having adverse effects or generally deteriorating following the procedure, but there has been little research on adverse effects of the screening examination. The few studies that have been published indicate that the procedure is painful and may result in harmful physiological changes. Adverse events that have been reported include changes in vital signs such as increased heart rate, and decreased oxygen saturation levels<sup>3-8</sup> The International Evidence-Based Group for Neonatal Pain<sup>9</sup> has included eye examinations for ROP in the list of painful procedures performed in the NICU.

Three small studies have reported additional systemic effects or adverse consequences of ROP examinations. One study found significant increase in heart rate ( $p=0.0272$ ) and significant decrease in oxygen saturation levels ( $p=0.0275$ ) in 30 infants immediately after the eye examination, but no significant changes in blood pressure, temperature, or respiratory rate. This study examined adverse effects during the eye examination itself and immediately afterwards, but did not follow the infants post procedure.<sup>10</sup> A second study examined 27 infants during eye screening for ROP and for 24 hours afterwards. Vomiting, increased gastric residuals, apnea, and need for increased respiratory assistance were reported; however, the incidence of these events did not significantly differ from the incidence before the examination<sup>11</sup> In addition, a case study of adverse events in two infants after eye examinations reported apnea and bradycardia during routine ROP screening.<sup>12</sup>

Mydriatic eye drops to dilate the pupils are routinely administered before ROP eye examinations. Cyclomydril, the mydriatic drug used in this study, is a combination of cyclopentolate 0.2%, an anticholinergic drug that inhibits the sphincter pupillae muscle and blocks pupil constriction, and phenylephrine 1%, an alpha-adrenergic drug that directly acts on the ciliary muscle to dilate the pupil.<sup>13</sup> Adverse effects directly related to systemic absorption of mydriatic eye drops have been documented following ROP screening.<sup>14</sup> Adverse effects of mydriatic drugs include feeding intolerance,<sup>15</sup> delayed gastric

emptying,<sup>16</sup> transient paralytic ileus associated with oxygen desaturation,<sup>17</sup> apnea and vomiting,<sup>18</sup> acute hypertension,<sup>19</sup> and neurological changes.<sup>20</sup>

There is beginning evidence that ROP examinations have systemic physiologic effects. Most of the research has focused on changes during the examination. However, no study has comprehensively examined adverse effects of ROP screening examinations over an extended period following the procedure. This pilot study therefore, examined the nature and frequency of physiologic changes and illness events in infants 2 days before and 2 days after routine eye examinations.

## Purpose

The primary purpose of the study of this pilot study was to monitor changes in infant health status and adverse physiologic events in the two days following ROP eye screening. Secondary purposes were to determine the need for continued research and to assess the feasibility of collecting the necessary data from patient charts.

## Methods

### Subjects

The sample consisted of 50 infants who were hospitalized in a children's hospital NICU and undergoing their first eye examination for ROP. Because of the paucity of information concerning physiologic effects of ROP examinations in neonates, there were no data on which to base power and sample size calculations. Therefore, calculations for confidence intervals and probabilities were based on research that studied adverse effects of eye examinations for ROP.<sup>10, 11</sup> With 50 infants, the exact binomial 95% confidence interval for the occurrence rate of an effect that was not observed would be (0%, 7%), so we are 95% confident that the occurrence rate of any adverse events not observed in the pilot study is no more than 7%. Also of interest was the probability of failing to observe a relatively rare event in the series of 50 infants. The probability of not observing any occurrences of an effect with an occurrence rate of 4% in 50 infants is 0.13 and of an effect with an occurrence rate of 5% or greater is less than or equal to 0.08. Since effects of interest were thought to have occurrence rates of greater than 4%, the likelihood of failing to observe at least one occurrence of these effects in the pilot sample was approximately 10% or less.

The IRB approved the study and gave an exemption from obtaining parental consent because the study was based on a medical record review of infants undergoing a routine procedure. The study included all infants identified by NICU health care providers to require screening for ROP based on unit protocol: a) less than 30 weeks gestational age at birth, b) weight of less than 1500 grams at birth, or c) identified by the neonatologist as having a history of clinical instability and therefore at high risk for ROP.<sup>16</sup> No eligible infants were excluded from the study during the period of data collection.

### Variables and their measurement

Infants who met the criteria for ROP screening were examined for the first time at 4–5 weeks of age by a pediatric ophthalmologist. A medical record audit was performed daily beginning 2 days before and ending 2 days after the eye examination, using a tool based on review of the literature and designed for this study to track parameters of respiratory, gastrointestinal, cardiovascular, and neurological status. Outcome variables are outlined in Table 3. Apnea events were defined as an absence of respirations for greater than 20 seconds. Nurses at the bedside either observed the apnea events directly or were notified by the monitor alarm that a period of apnea had lasted more than 20 seconds. Data were collected for each of the two days prior to the examination using information abstracted

from medical records. Data collected from medical records included birth weight, current weight, gestational age, postnatal age, race, gender, vital signs, oxygen saturation levels, lab results, intake and output, feeding history, adverse events, medications, and therapeutic procedures. Physiologic changes and illness events outlined in Table 3 were counted in 24-hour blocks of time starting 48 hours before the procedure and ending 48 hours after the procedure. The principle investigator (PI) and registered nurse research assistant (RA) collected data jointly on the first five infants. Inter-rater reliability checks were then performed on 10% of medical records drawn at random. All data entry was monitored and rechecked by the PI.

The Neonatal Therapeutic Intervention Scoring System (NTISS) was used to assess severity of illness once daily for 2 days before the ROP examination, the day of the examination, and 2 days after the procedure. The NTISS evaluates the following categories: respiratory, cardiovascular, drugs, monitoring, nutrition/metabolic, transfusion, procedural, and vascular access therapies. The NTISS assigns a severity-of-illness score that may range from 0 to 47. NTISS scores have been highly correlated with other markers of illness severity, and found predictive of NICU length of stay and total hospital charges. The NTISS is thus considered to be a valid indicator of therapeutic intensity and illness severity in neonates and was used in this study to evaluate any changes in illness severity after the eye examination.<sup>17</sup>

Gestational age at birth, postconceptional age, gender, and race were recorded to characterize the sample. The Neonatal Medical Index (NMI) is a tool that was designed to summarize an infant's medical course since birth and was used in this study to characterize the health/illness history of the sample. The NMI stratifies infants into five grades ranging from grade 1, infants who are well, to grade 5, infants who have undergone major medical problems and are at highest risk for serious complications. The NMI takes into account birth weight, problems such as the need for surgery or grade of intraventricular hemorrhage, and therapeutic procedures such as length of time on the ventilator.<sup>18, 19</sup>

## Results

The study continued over a period of 4 months until fifty infants had been screened. Demographic and medical characteristics of these infants are summarized in Table 4

NTISS scores indicated a trend toward improvement in health/illness status over five days, ranging from a mean of 14.84 two days before the eye examination to 13.2 on the day of the examination to 12.2 two days after the examination. Lower scores indicate decreasing severity of illness. There was no significant difference in the incidence of the following adverse events before and after the eye examinations: abdominal distention, bradycardia, tachycardia, capillary refill > 2 seconds, cyanosis, increases in gastric residual, clinical signs of seizure activity, or positive blood cultures indicating sepsis. There was a change in the frequency of apnea events after the eye examinations.

Apnea events were analyzed only for the 39 infants who were not ventilated during the study. McNemar's test for comparing paired proportions was used to analyze changes in the occurrence of apnea events for the 24 hour period before the eye examination and the 0–24 hour and 25–48 hour periods after the eye examination. The p-value from the exact distribution was calculated using StatXact<sup>®</sup> software (Cytel Inc., Cambridge, MA). Four infants had no apnea before the eye examination but experienced apnea in the first 24 hours after the examination. Eight infants experienced apnea in the 25–48 hour period after the eye examination. Six of these eight infants experienced new onset apnea in the 25–48 hour period, and two infants experienced apnea in the first 24 hours after the eye examination as well as in the 25–48 hour period. Compared to the period before the procedure, there was a

significant increase in the number of infants experiencing events ( $p=0.04$ ) in the 25–48 hour period after the eye examination. Table 5 presents changes in the frequency of apnea events after the ROP examinations. There were no statistically significant relationships between gestational age, weight, gender, race, or Neonatal Medical Index (NMI) grade and the frequency of having apnea events after the eye examination.

No infants required intubation and mechanical ventilation after the eye examination, although some infants required increased oxygen flow rates. There were no significant differences in the frequency of low oxygen saturation events  $<90\%$  (unit protocol) before and after the ROP eye examinations. However, secondary analysis using the Kruskal-Wallis test found a significant difference in the frequency of oxygen desaturation events between infants with and without apnea (0–24 hours after examination  $p<0.002$ , 25–48 hours after examination,  $p<0.001$ ).

## Discussion

The causes of physiologic changes such as apnea events following eye examinations are unknown. There may be adverse effects of the eye examination for ROP because (1) it is a painful procedure,<sup>3, 4, 7, 10, 11</sup> (2) it is a stressful procedure that overwhelms and exhausts the infant,<sup>20</sup> (3) the oculocardiac reflex may cause apnea and bradycardia during the eye examination<sup>14</sup> and (4) ophthalmic drops that have anticholinergic and alpha adrenergic properties may be absorbed with systemic effects.<sup>13, 21</sup>

When preterm infants experience severe or repetitive pain such as that associated with the ROP examination, there are immediate and long-lasting harmful consequences. Acute pain causes physiologic instability, including tachycardia and decreased oxygen saturation, and may also lead to sleep disturbances, feeding problems, and inability to self-regulate. Physiologic responses associated with eye examinations are immediate.<sup>3, 5, 22, 23</sup> However, the apnea events in this study were delayed, suggesting the possibility of other causes since there is no known association between acute pain and delayed apnea events

Physical manipulation of the eyeball with the introduction of a speculum, scleral indentation with a depressor, and traction on the rectus muscle may stimulate the vagus nerve, causing bradycardia and ectopic beats.<sup>14</sup> However, this phenomenon occurs during the actual procedure and therefore cannot account for apnea events 25–48 hours afterwards.

## Implications for practice

Health care providers must carefully monitor infants for changes in respiratory status, heart rate and blood pressure during and following eye examinations and be prepared to intervene with administration of oxygen or respiratory support as needed. It is also important to be aware that apnea may occur after the eye examination in infants who have not experienced any apnea in the two days before the examination or even in the first 24 hours after the examination.

Infants undergoing the examination need comfort care such as swaddling, pacifiers, and gentle holding. Pain management is important, and local anesthetic drops may not prevent or relieve pain associated with ROP eye examinations.<sup>24</sup> Sucrose 24% is effective for relieving pain during ROP examinations and can be administered via pacifier dips or with an oral syringe alongside a pacifier.<sup>9</sup> A pacifier dipped in 24% sucrose delivers approximately 0.2 ml of sucrose solution and is offered to the infant 2 minutes before the procedure for maximum effect. The dose may be repeated immediately before or during the procedure as needed up to three times.<sup>25</sup> Although pain management strategies are available for ROP eye

examinations, they may be inadequate<sup>26</sup> and continued efforts are needed to guide evidence based practice for relieving pain during this procedure.

This study was based on infants undergoing their first ROP eye examination. However, some infants may receive eye examinations every 2 weeks during their NICU stay, and sometimes they receive their final eye examination immediately before discharge or as an outpatient. Parents who are taking their infant home on the same day as an ROP eye examination must be taught to monitor for apnea and to perform infant CPR. Also, health care providers should use caution in discharging infants soon after eye examinations, and might consider timing these examinations to allow for 1 – 2 days of inpatient observation before sending an infant home.

### Implications for research

Infants are more susceptible to the effects of mydriatic agents because of their low weight and immature metabolism.<sup>27, 28</sup> When ophthalmic drops are absorbed through the nasal mucosa or conjunctiva, the medication enters the blood stream immediately and bypasses the first pass through the liver. However, occlusion of the nasolacrimal duct immediately following administration of drops may reduce systemic absorption of ophthalmic medications.<sup>27, 28</sup> Research is needed on the effectiveness of this technique to reduce systemic absorption of ophthalmic medications. Research should also be conducted on reducing the size of mydriatic drops to prevent possible adverse effects. Smaller drops have been found to be as effective as larger drops for dilating pupils and they provide the added benefit of reducing incidence of hypertension.<sup>28, 29</sup>

Research is needed on factors such as fatigue and the cumulative effects of stress and pain that may contribute to adverse events up to 48 hours after an eye examination. Research is also needed to identify factors such as weight, gestational age, medical history and use of medications such as proparacaine 1% local anesthetic eye drops that may also contribute to adverse events following the eye examination.<sup>28</sup>

Increased gastric residual and feeding intolerance with emesis and abdominal distention were not significant in this study, but have been documented following cyclopentolate administration. Duodenal motor contractions may decrease fourfold following instillation of mydriatic drops.<sup>30</sup> Clearly, additional research is needed to examine possible changes in gastrointestinal function.

Limitations of this study include collecting vital sign data indirectly from medical records instead of directly from infants and not recording oxygen administration (FiO<sub>2</sub>) changes before and after the eye examination. It is recommended that in future studies, vital signs be taken directly from infants or from central monitors, and that changes in oxygen requirements (FiO<sub>2</sub>) be analyzed.

The generalizability of this pilot study is limited by the small sample and the focus on infants undergoing their first eye examinations. Studies with larger samples and with infants undergoing repeat eye examinations are needed to identify the causes of physiologic changes and illness events after ROP examinations, specifically focusing on causes of problems such as apnea. Health care providers can then develop interventions needed to prevent adverse consequences such as apnea, and thus provide guidelines for infant care during and after ROP eye examinations.

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**Table 1**

Recommended Timing of Initial ROP Eye Examination for Infants Born at 30 Weeks Gestational Age or Less

Gestational age at birth (weeks)	Chronological age at initial examination (weeks)	Adjusted gestational age at initial examination (weeks)
22	9	31
23	8	31
24	7	31
25	6	31
26	5	31
27–30	4	31–34

Based on joint recommendations of the American Academy of Pediatrics, American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus, 2006.

**Table 2**

## Unit Protocol for ROP Eye Examinations

<ul style="list-style-type: none"><li>• Pupils dilated with mydriatic ophthalmic drops (Cyclomydril (cyclopentolate 0.2%, phenylephrine 1%) 1–2 hours before the ROP eye examination.</li><li>• Schedule and dosage for Cyclomydril: two drops in each eye every 5 minutes for a total of three doses.</li><li>• During instillation of eye drops, cardiorespiratory monitors are in use with alarms on.</li><li>• Topical anesthetic eye drops proparacaine hydrochloride 0.5% are administered immediately before the ROP eye examination</li><li>• During the eye examination, the infant is swaddled and offered a pacifier. Sucrose 24% 1 pacifier dip every 2 minutes X 3 may be offered.</li><li>• A speculum is used to retract and hold the eyelids open during the examination</li><li>• A depressor is used to move the eyeball into required positions while the ophthalmologist examines the retina of the eye with an ophthalmoscope. Each eye is examined separately.</li><li>• The infant is monitored continuously for signs of distress. If problems occur, the examination is stopped and the infant is stabilized.</li><li>• Following the examination, the infant continues to be monitored for heart rate and respiratory status.</li></ul>
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NOTE: protocol for ROP eye examinations varies according to NICU policy

**Table 3**

## Variables Examined Before and After ROP Eye Examinations

Abdominal distention
Apnea > 20 seconds
Bradycardia < 90 beats per minute
Tachycardia > 180 beats per minute
Capillary refill > 2 seconds
Central cyanosis
Documented increases in gastric residual in ml
Documented signs of seizure activity
Sepsis documented with positive blood culture
Oxygen saturation < 90%

**Table 4**

## Infant Demographic Characteristics and Medical History

Mean (std dev) gestational age at birth	28.24 (2.62) weeks
Range	23 – 36 weeks
Mean (std dev) post-conceptional age at exam	32.82 (2.84) weeks
Range	27–40.5 weeks
Mean (std dev) birth weight	1161 (352) grams
Range	480–1918 grams
Mean (std dev) current weight	1652.5 (515) grams
Range	570 – 3226 grams
Gender	27 male (54%) 23 female (46%)
Race/ethnicity	African American - 18 (36%) White – 24 (48%) Hispanic – 6 (12%) Biracial – 2 (4%)
Neonatal Medical Index Korner AF, Stevenson DK, Kraemer HC, et al. Prediction of the development of low birth weight preterm infants by a new neonatal medical index. <i>J Dev Behav Pediatr</i> 1993;14:106–11.	
Grade I – well infant	Grade I - 0
Grade II – Assisted ventilation <48 hours	Grade II – 7 (14%)
Grade III – Assisted ventilation 3–14 days*	Grade III – 10 (20%)
Grade IV – Assisted ventilation 15–28 days*	Grade IV – 15 (30%)
Grade V – Assisted ventilation > 29 days*	Grade V – 18 (36%)

\* and/or intraventricular hemorrhage, major illness, major surgery, low birth weight

**Table 5**

Changes in frequency of apnea events after ROP Examination in 39 infants not on ventilation

		Apnea 0–24 hours after eye examination?	
		No	Yes
Apnea before Eye examination? p=0.13	No	30	4
	Yes	0	5
		Apnea 25–48 hours after eye examination?	
		No	Yes
Apnea before Eye examination? p=0.04	No	26	8
	Yes	1	4

p-values are based on McNemar's test for paired proportions