

Practice Patterns in Ophthalmic Examinations for Retinopathy of Prematurity in the United States

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Abstract

Purpose: To assess the types of dilating drops used, their perceived safety and the need to monitor preterm infants with retinopathy of prematurity during eye examinations.

Methods: A national survey was sent via e-mail to pediatric ophthalmologists, pediatric retina specialists and neonatologists. The survey was sent to 1564 members of the American Association for Pediatric Ophthalmology and Strabismus (AAPOS), 42 pediatric retina specialists, and 209 neonatologists.

Results: Of 86 responders (29 retina specialists, 33 pediatric ophthalmologists, 24 neonatologists), most used cyclopentolate/phenylephrine (cyclomydril™) combination drops. 29% of neonatologists reported serious side effects from dilating drops compared to 8% of ophthalmologists. 50% of neonatologists compared to 6% of ophthalmologists expressed the need to monitor some infants' vital signs during dilated eye examinations.

Conclusions: Perceptions about the need to monitor vital signs and the safety of dilating drops during ROP examinations differ between ophthalmologists and neonatologists.

Keywords: Retinopathy of Prematurity; Dilating drops; Dilated fundus exams; Topical mydriatics; Neonatal eye exams; Eyelid speculum examination

Abbreviations: (ROP): Retinopathy of Prematurity; (NICU): Neonatal Intensive Care Unit; (ICU): Intensive Care Unit; (ER): Emergency Room; (RDS): Respiratory Distress Syndrome; (NEC): Necrotizing Enterocolitis; (GI): Gastrointestinal ; (CNS): Central Nervous System ; (IOP): Intraocular Pressure ; (CPR): Cardiopulmonary Resuscitation

Introduction

Retinopathy of prematurity (ROP) is a disease characterized by abnormal retinal angiogenesis in preterm infants. It is characterized by a delay in physiologic retinal blood vessel development followed by proliferation of abnormal vessels into the vitreous, which can result in retinal detachment and blindness [14]. In the US, national recommendations in the form of a joint statement by the American Academy of Pediatrics – Section on Ophthalmology, American Academy of Ophthalmology and American Association of Pediatric Ophthalmology and Strabismus, and the American Association of Certified Orthoptists provide the framework for ROP screening [1]. Individual neonatal Intensive Care Units (ICUs) may modify these criteria based on their experiences as well as in specific cases, when a neonatologist feels an eye examination is warranted. The burden of eye examinations is significant, and each examination requires pupillary dilation of both eyes. Infants are often swaddled; then after application of topical anesthetic, a lid speculum is placed in each eye and the eye is manipulated using a scleral depressor or similar instrument to examine the peripheral retina and perform scleral depression. Alternative

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approaches using contact cameras to obtain fundus images also require topical anesthetic and swaddling [15]. Examinations often need to be continued even after discharge from the NICU, on an outpatient basis, until the retina is fully vascularized, or the overall risk of developing treatment requiring ROP becomes negligible [41].

There have been some systemic side effects reported in infants from topical mydriatics, apart from the stress of the examination itself, although other studies report that mydriatics are safe to use [6-13]. Though the safety and efficacy of several dilating regimens are discussed, there is not a uniform recommendation across the literature as to what drops should be used in infants [7,9,12].

The Table below briefly reviews the topical medications commonly used for pupillary dilation in ROP exams, their mechanism of action and potential side effects, as well as published data in neonates, if available.

Medication Name	Mechanism of Action	Potential Side Effects	Data in Neonates
Phenylephrine hydrochloride (AK-Dilate®, Akorn, Somerset, NJ; Mydrin®, Alcon, Ft. Worth, TX) peripheral retina	Adrenergic, Stimulates the dilator pupillae muscle	Tachycardia, hypertension, arrhythmia, headache, hyperhidrosis	Increased mean arterial pressure, can cause gastric dilation and paralytic ileus ^{2,3,5}
Cyclopentolate (Cyclogyl)	Anticholinergic, blocks the responses of the sphincter pupillae and ciliary muscle to cholinergic stimulation	Behavioral changes, seizures, GI disturbance, increased IOP	Can cause NEC in infants ⁴ , CNS depression
Tropicamide	Anticholinergic, blocks the responses of the sphincter pupillae and ciliary muscle to cholinergic stimulation	CNS disturbances, psychotic reactions, Increased IOP	Side effects usually attributed to drugs used in combination with tropicamide ²

All Data from Physician's Desk References (PDR) unless otherwise notes.

Table 1: Commonly Used Mydriatics in Infants and Reported Side Effects.

In the ophthalmic literature, there have been several studies that report conflicting results as to the relationship of an infant's adrenergic response to either the stress of the physical manipulation of the globe and eyelid speculum placement or to mydriatic eye drop instillation during an examination for ROP [6, 10,11]. Laws, *et al.* and Clarke, *et al.* reported elevations in blood pressure after eye drop instillations, but Rush, *et al.* reported no effect after eye drops were given. In all three studies, bradycardia and decreased oxygen saturation occurred during the eye examinations.

Another question that has not previously been addressed in the literature is the safety of performing examinations for ROP in the outpatient setting, where unlike in the NICU, there is no continuous monitoring of vital signs. This question arose in our practice after an infant suffered a significant episode of bradycardia and apnea that necessitated admission to the hospital, where he was newly diagnosed with pulmonary hypertension and hypoxia.

In this study, we sought to investigate the current practice patterns in pharmacologic topical mydriasis in neonates as well as the perceived safety of dilating drops and the need for monitoring of infants during outpatient ROP examinations.

Materials and Methods

A 10-question survey was developed to address perceptions regarding the safety of the commonly used dilating drops as well as the level of monitoring necessary for infants examined for ROP in the out-patient setting. The full survey was designed for pediatric ophthalmologists and pediatric retina specialists (Figure 1) and a shorter version lacking questions on eye examination techniques was developed for neonatologists (Figure 2). Physicians from these specialties were identified through the American Association for Pediatric Ophthalmology and Strabismus (AAPOS), the Association of Pediatric Retina Surgeons, and neonatologists from university programs

and local hospitals throughout the country (as the American Academy of Pediatrics does not allow distribution of on-line surveys to its membership).

1. Are you a:
 - A) Pediatric Ophthalmologist
 - B) Retina Specialist
 - C) Trained in both pediatric ophthalmology and retina
2. Do you perform ROP screening exams and/or laser therapy for ROP patients?
 - A) Yes
 - B) No
3. What drops do you routinely use to achieve pupillary dilation in your NICU patients?
 - A) Cyclomydril (cyclopentolate 0.2% and phenylephrine 1%)
 - B) Phenylephrine 2.5% (mydrin) + tropicamide 1% (mydracyl)
 - C) Cyclopentolate 1% (Cyclogyl)
 - D) Other (please specify agent and concentration)
4. Do you perform vitreoretinal surgery in infants (< 1 year old)?
 - A) Yes
 - B) No
5. If yes, what drops do you use routinely to achieve adequate pupillary dilation in retina surgery?
 - A) Cyclomydril (cyclopentolate 0.2% and phenylephrine 1%)
 - B) Phenylephrine 2.5% (mydrin)+ tropicamide 1% (mydracyl)
 - C) Cyclopentolate 1% (Cyclogyl)
 - D) Other (please specify agent and concentration)
6. Do you examine infants (<1 year old) in the outpatient setting?
 - 1) Yes
 - 2) No
7. What drops do you routinely use to achieve adequate pupillary dilation in outpatient setting?
 - A) Cyclomydril (cyclopentolate 0.2% and phenylephrine 1%)
 - B) Phenylephrine 2.5% (mydrin) + tropicamide 1% (mydracyl)
 - C) Cyclopentolate 1% (Cyclogyl)
 - D) Other (please specify agent and concentration)
8. Have any of your infant patients ever experienced a major side effect while in your care. Major side effects include seizure, cardiovascular collapse requiring resuscitation?
 - 1) Yes
 - 2) No
9. Do you feel this side effect was due to the dilating drops (as opposed to other factors such as stress of exam, lid speculum placement, vagal reflex, etc)?
 - 1) Yes
 - 2) No
10. Do you monitor patient's vitals prior, during or after an eye exam?
 - A) Yes, only prior
 - B) Yes, prior and during
 - C) Yes, prior, during and after
 - D) No

11. Do you think vital signs should be monitored in infants when seeing the ophthalmologist?
- A) Yes
 - B) No
 - C) Other (please specify)

Figure 1: Survey Sent to Ophthalmologists (Pediatric Ophthalmologist and Pediatric Retinal Specialists).

1. What dilating drops are routinely ordered for eye examination on infants in your Neonatal Intensive Care Unit (NICU)?
- A) Cyclomydril (cyclopentolate 0.2% and phenylephrine 1%)
 - B) Phenylephrine (2.5%) and tropicamide 1% (mydriacyl)
 - C) Cyclopentolate 1% (cyclogyl)
 - D) I don't know
 - E) Other. Please specify
2. Who orders the dilating drops for the eye exams?
- A) Attending neonatologist (or a member of the NICU team)
 - B) Ophthalmologist (or a member of the ophthalmology team)
 - C) Other. Please specify
3. Have you ever experienced a major adverse event that you believe was due to the dilating drops (not the stress of the exam)?
- A) None Seizure
 - B) Apnea-bradycardia
 - C) Cardiopulmonary collapse requiring resuscitation
 - D) Abdominal distension
 - E) Other. Please specify
4. Do you feel infant's vitals should be monitored during eye examinations in the outpatient setting?
- A) Yes
 - B) No
 - C) Other. Please specify
5. Do you feel ophthalmologists are qualified to interpret vital sign measurement on infants undergoing ophthalmic examination in the outpatient setting and initiate corrective measures?
- A) Yes
 - B) No
 - C) Other. Please specify

Figure 2: Survey Sent to Neonatologists.

An invitation to participate in the survey was sent by e-mail through the SurveyMonkey™ website (www.surveymonkey.com). No personal or institutional data were collected.

The survey was sent to 1564 members of AAOPOS, 42 pediatric retina specialists, and 209 neonatologists. Respondents who reported no direct involvement in care for ROP were excluded from the analysis.

Results and Discussion

The self-reported subspecialty of the 86 respondents was: pediatric retina specialist (n = 29), general pediatric ophthalmology (n = 33), neonatology (n = 24). The response rate for each of the sub-specialties was: pediatric retina specialist 69% (29/42), general pediatric ophthalmology 2.1% (33/1564), neonatology 11.48% (24/209).

Dilating Drops

Neonatologists ordered dilating eye drops for infants undergoing ROP examinations 60% of the time. Fifty two percent of neonatologists reported that cyclomydril (cyclopentolate 0.2% and phenylephrine 1% combination drop) was their preferred dilating drop regimen in the NICU, whereas 13 percent reported cyclomydril and tropicamide 1% (Figure 3A). Up to 30% of neonatologists who responded to the survey did not know what drops were used in their NICU to achieve pupillary dilation. Sixty five percent of neonatologists reported no serious side effects associated with dilating drops. In those who reported serious side effects, they reported apnea/bradycardia episodes (21%), cardiopulmonary arrest requiring CPR (8%) and abdominal distention (4%).

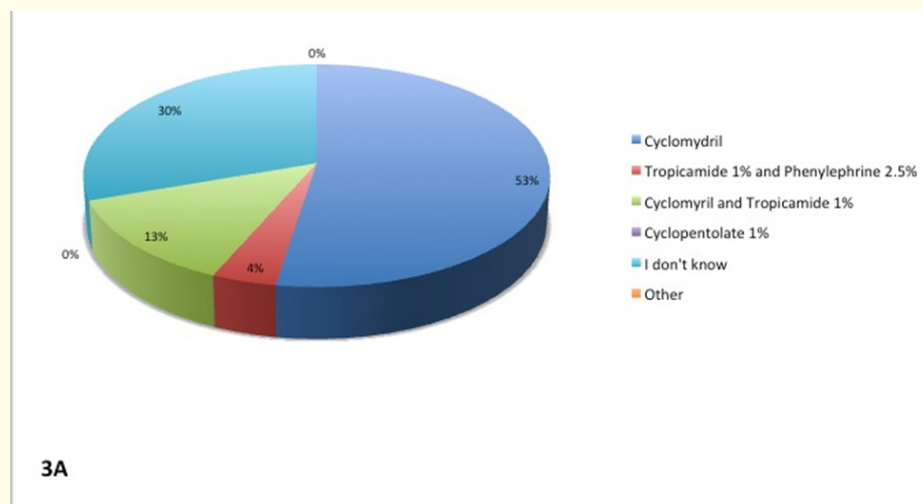


Figure 3A: Mydriatic Use Reported by Neonatologists in the NICU.

Of the respondents who were ophthalmologists, 66% reported that cyclomydril was used for pupillary dilation, whereas 22.5% reported a combination of tropicamide 1% and phenylephrine 2.5% (Figure 3B). There was a similar distribution in outpatient drop use; however, ophthalmologists more often added tropicamide 1% in addition to cyclomydril (Figure 3C). In contrast to the neonatology respondents, 80.6% of ophthalmologists reported no adverse effects from dilating drops in the infants they examined.

Based on the results of our study there was a clear difference in the perception of safety of dilating drops between neonatologists and ophthalmologists. One possible explanation is that in the ophthalmic literature and practice, the individual contribution of the dilating drops themselves versus the stress of the exam have been considered and though the results on the effects of the drops themselves are conflicting, the effect of globe manipulation and speculum placement is a significant stressor across all studies. However, neonatologists may be concerned with the overall condition of the infant during the whole process of eye dilation and examination and may not distinguish adverse events due to one or the other. Another possibility is that ophthalmologists are involved in the infant's care at a discrete time interval, immediately surrounding the eye examination, whereas neonatologists spend more time in the NICU monitoring the clinical picture as it evolves throughout the day and night. Some adverse effects may not arise until a few hours after instillation of eye drops, and the ophthalmologist may not be aware of these events.

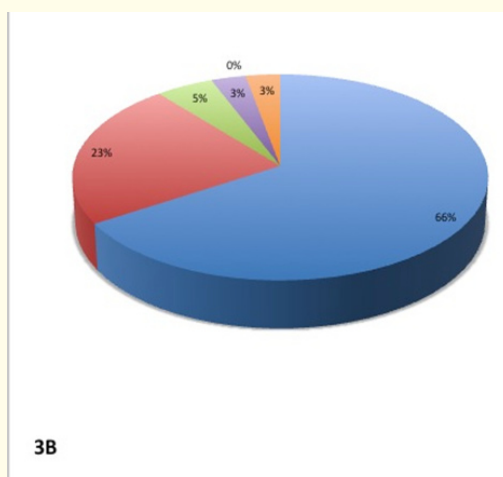


Figure 3B: Mydriatic Use Reported by Ophthalmologists in the NICU.

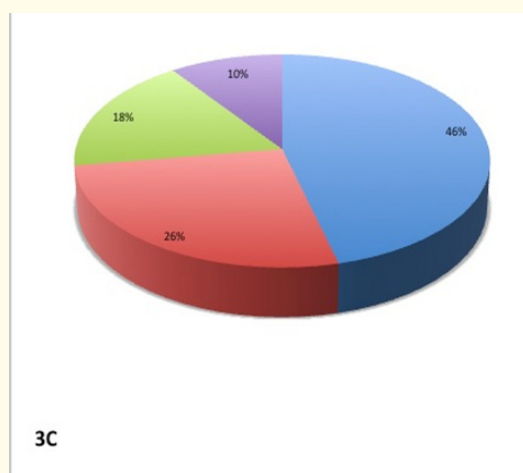


Figure 3C: Mydriatic Use Reported by Ophthalmologist in the Outpatient Setting.

Though it is clear that the mydriatic drops can have significant side effects in infants, there is no consensus between ophthalmologists and neonatologists as to the severity and frequency of systemic side effects. At the very least, this is an area that requires further discussion across the specialties, and further study to understand what the real risks of dilating drops in infants' eyes are.

Need for monitoring

Neonatologists were asked if vital signs should be monitoring during ROP examinations in the outpatient setting. Thirty-four percent indicated that vital signs should be monitored, and 13% believed that the decision to monitor an infant depended on the gestational age and comorbidities. Thirty percent indicated that vital signs should not be monitored, and 21% responded that they did not know (Figure 4). When neonatologists were asked the question whether if they believed ophthalmologists were qualified to interpret abnormal vital signs in infants and initiate corrective measures, 47% of neonatologists responded "No", 34% responded "Yes" and 17% responded "Unsure".

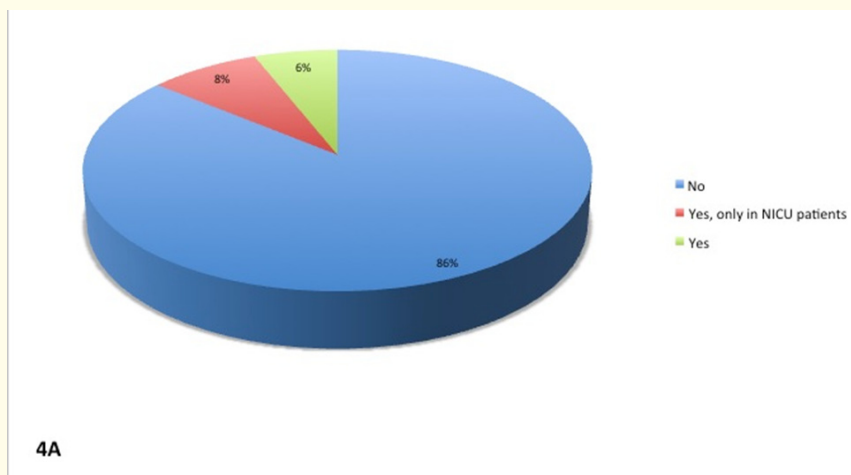


Figure 4A: Should Vital Signs Be Monitored in the Outpatient ROP Exam? Neonatologists.

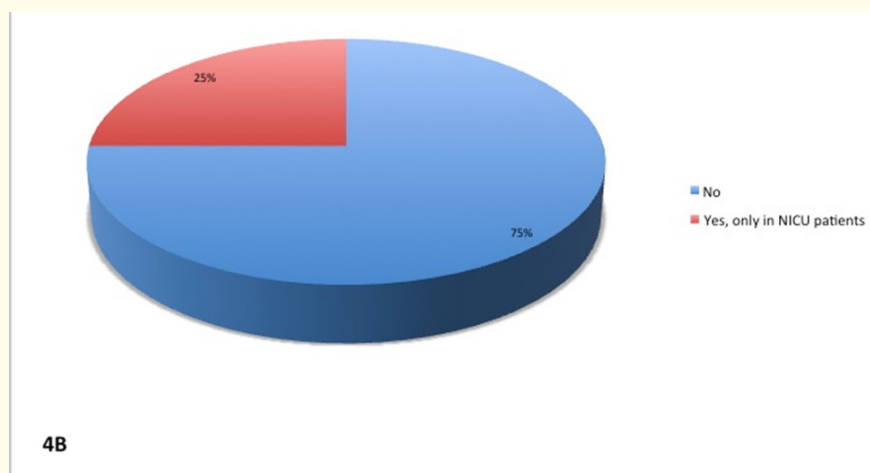


Figure 4B: Should Vital Signs Be Monitored in the Outpatient ROP Exam? Ophthalmologists.

When asked about monitoring vital signs during ROP exams, 75% of ophthalmologists reported that they do not monitor vital signs, and 25% reported monitoring vital signs only in the NICU setting. Eighty six percent of ophthalmologists did not believe vital signs should be monitored, whereas 8% believed that vital signs should only be monitored in the NICU setting but not as outpatient, and 6% believed that vital signs should not be monitored.

The results from this portion of the survey are revealing. In our cohort of respondents, vital signs are not monitored during outpatient ROP examinations, but should they be? Almost half the neonatologists surveyed believed that vital signs should be monitored at least in select cases (such as infants born at younger gestation ages or those with significant medical comorbidities). The next logical question is if vital signs should be monitored, are ophthalmologists qualified to interpret abnormal results and respond appropriately?

In one of our practices (AS, JS and AJ), we instituted a policy of checking an infant's vital signs prior to instillation of the first set of dilating drops. In select cases, for example, infants with severe Respiratory Distress Syndrome (RDS) and persistent dependence on supplemental oxygen, vital signs are monitored continuously throughout the examination. Since beginning this policy 6 months ago, we transferred 4 infants to the Emergency Room for hypoxia and bradycardia based on the initial set of vital signs prior to pupillary dilation and examination, and all 4 were admitted to the intensive care unit. Furthermore, due to the frequency of these events, we now physically conduct the ROP examinations in the high risk neonatology clinic and are at all times in close proximity to an experienced neonatologist.

Based on the experience in our institutions, preterm infants may be medically unstable when receiving an examination for ROP for a number of reasons unrelated to eye drop use or funduscopic examinations, such as chronic hypoxia due to undiagnosed pulmonary hypertension as occurred in two of our cases. If baseline heart rate, blood pressure and oxygen saturation are not assessed, bradycardia and apnea may be erroneously attributed to dilating drops and the stresses of the eye examination. If an infant is not medically stable to undergo an ROP examination, that infant should receive urgent medical attention prior to attempting an examination.

In our clinical experience ophthalmologists are able to interpret abnormal results when it came to infants' vital signs and initiate a code, or rapid medical response.

Despite sending the survey to a large number of physicians, the response rate was low. Nonetheless, the information obtained in the survey provides interesting differences in perceptions between ophthalmologists examining infants with ROP and neonatologists caring for infants undergoing eye examinations for ROP. Further approaches to assess the perceptions among neonatologists and ophthalmologists should be considered. The approaches used in our institutions are specific to our patient populations and may not be feasible or generalizable to other practices.

Conclusion

Our study revealed a difference in the perception of safety of mydriatic eye drop use for ROP examination in the outpatient setting between ophthalmologists and neonatologists. We also found that infants' vital signs are not monitored in the outpatient setting for ROP examinations; however, a substantial portion of neonatologists who responded to the survey believed vital signs should be monitored. Further collaboration and investigation across the specialties is needed to determine the incidence and frequency of adverse effects of dilating drops and the optimal level of monitoring during ROP exams.

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