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The Pain Response to Mydriatic Eye Drops in Preterm Infants

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Abstract

Objective—Evaluate physiologic and behavioral pain responses of premature infants following instillation of mydriatic eye drops for ROP examinations. While burning and stinging occurs in older patients, the infant pain response is not well characterized.

Study Design—Vital sign and video monitor recorded infant responses before, during, and after mydriatic (tropicamide 1%, phenylephrine 2.5%) administration upon first ROP exam. Two masked observers graded Premature Infant Pain Profile (PIPP) scores immediately prior and following eye drop administration. Scores <7 indicate no/minimal pain, 7-12 slight/moderate, >12 severe.

Results—Twenty infants had mean pre-mydriatic PIPP score 3.6 (SD 1.6), mean post-mydriatic score 5.7 (SD 3.4), mean change 2.1 (SD 3.4)($p=0.01$). One (5%) had pre-mydriatic PIPP score 7, seven (35%) post scores ≥ 7 ($p=0.07$) with one >12.

Conclusions—Mydriatic drops cause a clinically significant pain response in one third of infants. Non-pharmacologic supportive measures are recommended for all infants until predictive factors are defined.

Keywords

retinopathy of prematurity

Ophthalmologic examinations for retinopathy of prematurity (ROP) and other conditions are common in the newborn intensive care unit (NICU). Adequate retinal examinations typically

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CONFLICTS OF INTEREST

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require pharmacological dilatation of the pupils with mydriatic eye drops, inspection with an indirect ophthalmoscope, and, in some cases, the use of an eyelid speculum to adequately keep the eyelids open and scleral depression, a technique in which an instrument is directly applied to the surface of the eye in order to rotate and compress the globe for optimal visualization.

Studies of infants undergoing eye examinations have demonstrated signs consistent with pain. Infants may have decreased oxygen saturations and increased heart rates during the exam,¹ and a subset of infants demonstrated persistent changes on a standardized neonatal pain assessment scale (CRIES) even 24 hours after examination.² The use of lid speculums and scleral depression appear to be the strongest painful stimuli.³ Based on these findings, the American Academy of Pediatrics recommends that measures be taken to reduce pain during eye examinations.⁴ Such measures might include swaddling, topical anesthetics, pacifier use, and oral sucrose.⁵⁻⁹

Infants may experience pain not only from the eye examination itself, but also from the mydriatic drops that are administered in preparation for the examination. Based upon routine clinical use by ophthalmologists, it is known that mydriatics such as tropicamide and cyclopentolate cause burning or stinging upon application to the ocular surface. Formal studies in adults and adolescents confirm a transient but significant amount of discomfort associated with mydriatic drops.¹⁰ Premature infants cannot verbalize pain and may have pain thresholds that are lower than those of older children and adults. In infants, mydriatic eye drops have been associated with a rise in blood pressure at the time of drop instillation that may persist until and through the ophthalmologic examination, which typically occurs 30-60 minutes later.^{1, 11} However, formal data using masked assessments and a standardized assessment scale are limited, and studies including behavioral measures of pain have not been reported. In addition, variations among nurses in the manner in which eye drops are instilled into the eyes is a potential confounding factor. Clinical observation suggests that there is significant variety in the technique, force, and degree to which eyelids are opened, all of which may affect the observed pain response.

We sought to investigate the pain response to mydriatic eye drops expressed by premature infants, using masked formal assessments and controlling for the technique of drop installation. With the aid of an FDA approved neonatal bedside monitor (The CNS Neonatal Neurological Monitor, Moberg Research, Ambler, PA), we had the capability to videotape, measure, record, and analyze multiple simultaneous physiologic and behavioral parameters to assign masked Premature Infant Pain Profile (PIPP) scores to infants undergoing mydriatic drop instillation prior to ophthalmologic examinations. The video data was also used to observe the manner in which the drops were administered to the infants.

PATIENTS AND METHODS

Infants admitted to the Neonatal Intensive Care Unit at Pennsylvania Hospital in Philadelphia, Pennsylvania were prospectively enrolled in the study from February 2011 to September 2011. Infants were eligible for the study if they met birth weight (> 1501 g) or gestational age (> 32 weeks) criteria for retinopathy of prematurity examinations. Infants

were excluded from the study if they had any known neurological abnormalities, seizures, or other conditions that could alter pain response, or if they had corneal abrasions or ulcers. Informed consent was obtained from at least one parent of each subject. The study was approved by the joint Institutional Review Board of the Hospital of the University of Pennsylvania and Pennsylvania Hospital, and was carried out in compliance with the principles of the Declaration of Helsinki and the United States Health Insurance Portability and Accountability Act.

At the study hospital, infants typically received three sets of mydriatic eye drops (1 drop of tropicamide 1% and 1 drop of phenylephrine 2.5%) over a 30 minute period prior to examination. It was not our standard practice to administer, and the study infants did not receive, proparacaine hydrochloride, a topical anesthetic, prior to the mydriatic eye drops, because proparacaine itself may sting, requires additional eyelid manipulation, and is not of established benefit in this population. Each study infant was evaluated during the administration of the first set of mydriatic eye drops for his or her first retinopathy of prematurity examination in an effort to obtain data without the confounding effect of priming, memory or habituation from the prior receipt of mydriatic drops. The drops were given by the clinical nurse caring for the child that day, and no study-specific education on the instillation of eye drops was provided. No premedication, including sucrose, was given to any infant. Drop order was not specified for the study. The CNS Neonatal Neurological Monitor (Moberg Research, Ambler, PA) was used to videotape the encounter and record physiologic data (heart rate, pulse oximetry, respiratory rate) indirectly via cables connected to each infant's bedside monitor. A video camera attached to the CNS monitor was positioned to capture each infant's facial activity. The monitor was put in place prior to eye drop administration in order to obtain at least 30 seconds of baseline behavioral and physiologic data on each infant. It remained in place and continued to record data throughout and for at least 1 minute after eye drop administration.

Pain assessments were carried out using the Premature Infant Pain Profile (PIPP).¹²⁻¹⁴ The PIPP score evaluates 5 indicators of pain and also includes 2 modifying factors. The pain indicators are change in heart rate, change in oxygen saturation, brow bulge, eye squeeze and nasolabial furrow. Blood pressure is not a component of the PIPP score. The modifying factors are gestational age and behavioral state. A PIPP score ≥ 7 is an accepted indicator for the presence of pain.¹²⁻¹⁴ A score of 7 to 12 typically signifies pain for which clinicians might consider non-pharmacological intervention, while a score >12 suggests severe pain requiring medication. The maximum score is 21. The video clips for each subject were edited to separate the pre-mydriatic, post-mydriatic, and eye drop administration data. Two independent observers, one neonatologist and one pediatric ophthalmologist, masked to whether the data were obtained before or after mydriatic administration, reviewed the video data from the CNS monitor and assigned scores for the behavioral component of the PIPP score at baseline and immediately following mydriatic eye drop administration. Scoring was based on 30 second clips of video for both periods, as per PIPP scoring guidelines. This information was combined with the physiologic data obtained from the CNS monitor over the same time period to determine the infant's full pre- and post-mydriatic PIPP scores for each observer. For the purpose of data analysis, the PIPP scores from each masked observer were then averaged to calculate one pre-mydriatic and post-mydriatic score for each infant.

After all masked assessments were completed, both observers independently reviewed the video clips of eye drop administration and rated the force and manner in which the eyelids were opened as mild, moderate, or severe.

The difference between pre- and post-mydriatic PIPP scores was compared using a paired t-test. McNemar's exact test was used to compare the percent of infants experiencing pain (PIPP ≥ 7) between pre- and post-mydriatic administration. A test of linear trend was performed to test the association between the degree of eyelid manipulation and change in PIPP score. Agreement between the two observers' PIPP score ratings were assessed by using the intraclass correlation coefficient. A sample size of 20 infants provided a power of 87% to detect a mean change in PIPP score of 3 with a standard deviation of 4 and significance level of 0.05. These conservative assumptions were based upon prior studies, in which PIPP score changes associated with pain ranged from 3 to 6, with standard deviations of 1.5 to 4. Statistical analyses were completed using SAS statistical software v9.2 (SAS Inc, Cary, NC).

RESULTS

Twenty infants were enrolled in the study (Table 1). Slightly more than 50% of infants had previously received mechanical ventilation, though none were intubated at the time of study evaluation. Forty percent had been treated for suspected bacterial sepsis during their neonatal course. The majority of infants had no history of intracranial bleeding. None of the infants received sedating or pain medications within 48 hours of the examination. At the time of evaluation, the mean corrected gestational age was 33 4/7 weeks.

The mean pre-mydriatic PIPP score was 3.6 (SD 1.6) and the mean post-mydriatic PIPP score was 5.7 (SD 3.4), with a mean change in PIPP score of 2.1 (SD 3.4; $p=0.01$). Figure 1 depicts the pre- and post-mydriatic PIPP scores for each infant. Of the 20 infants, 1 (5%) had a pre-mydriatic PIPP score of 7 or greater, indicating the presence of pain, while 7 (35%) infants had a post-mydriatic PIPP score of 7 or greater ($p=0.07$), only one of whom had a score greater than 12, which is indicative of severe pain. There was high agreement between the two observers with regard to assignment of PIPP score. PIPP scores were within 1 point of each other in 36 (90%) of 40 pairs of ratings (20 pairs each for pre- and post-mydriatic score). The intraclass correlation coefficient between the two observers was 0.86 (95% CI: 0.68 – 0.94) for pre-mydriatic score, 0.95 (95% CI: 0.89 – 0.98) for post-mydriatic score, and 0.97 (0.92 – 0.99) for difference between pre- and post-mydriatic PIPP score.

When evaluating the change for each component of the PIPP score, the largest change was found for a decrease in oxygen saturation, with a mean PIPP score change of +0.85 for the 20 infants (maximum possible change for a single component is +3). With regards to the other indications, increase in heart rate had a mean score change of +0.45, brow bulge +0.4, eye squeeze +0.5, and nasal furrow +0.35.

The administration of eye drops was rated as mild for 8 infants, mild-moderate for 6 infants, moderate for 2 infants, and moderate-severe for 4 infants. The change of PIPP score increased with increasing eye manipulation, with mean PIPP score change 0.5 for mild

manipulation, 2.7 for mild-moderate manipulation, and 3.6 for moderate or moderate-severe manipulation (linear trend $p=0.10$).

DISCUSSION

We found that instillation of 2.5% phenylephrine and 1% tropicamide resulted in a pain response in only one third of premature infants undergoing their first retinopathy of prematurity examination. While there was a statistically significant increase in mean PIPP score for the cohort studied, the mean post-mydriatic score was only 5.7. This score falls within the range of “no pain” on the PIPP scale, so for most infants the eye drops did not cause a clinically significant pain response. However, 7 infants did experience pain post mydriatic drops, 1 of whom experienced severe pain. These findings suggest that appropriate comfort measures (swaddling, containment, non-nutritive sucking, positioning) during the course of mydriatic administration may be beneficial for a minority of infants.

Though we did not study the premature infant pain response to each eye drop individually, extensive clinical experience with adults and children in outpatient ophthalmology clinics indicates that tropicamide stings upon installation and phenylephrine typically much less so or not at all. Hassler-Hurt et al. found that 1% tropicamide caused pain in a group of 30 subjects, using a subjectively reported FACES scale.¹⁰ These investigators found that although the perceived pain with 1% tropicamide was consistently higher than 0.5% tropicamide, 33% of adolescents found the instillation of either concentration to produce “quite a lot of pain.”¹⁰ Unfortunately, an anticholinergic agent, such as tropicamide, is necessary to obtain adequate pupillary dilatation; phenylephrine alone will not suffice. Another commonly used anticholinergic agent in premature infants is 0.5% cyclopentolate.

Post-mydriatic PIPP scores potentially reflect an effect of both the mydriatic drops and the manner in which the drops were given. In this study, we found a linear trend for increasing PIPP score with increasing degree of eyelid manipulation. There were some inconsistencies in these data; for example, the infants with the smallest and largest change in PIPP score were both rated by our observers to have moderate-severe manipulation of the eyelids. Thus, the infants with the largest change in PIPP score and the infants who were rated to have moderate or moderate-severe manipulation did not necessarily overlap. However, the full pain response to eyelid manipulation may not be completely reflected in the PIPP scores, because the pre- and post-mydriatic video clips were edited to ensure that the observers were kept masked to any sign of eyelid manipulation or eye drop administration. Clinically, we have observed that there is wide variation in the rigorousness with which the eyelids are manipulated during eye drop administration in the NICU. Some of this variation may be due to the baseline state of the infant and how much he or she struggles to resist the drops, and some may reflect the nurse’s training or comfort. The eyelid skin is very thin and sensitive to manipulation. Strong force is not required to separate the lids, and they do not need to be widely spread for the drops to reach the ocular surface. Making an effort to minimize manipulation of the eyelids while giving eye drops is a simple and in our opinion important measure for anyone administering eye drops to infants or children.

Strengths of our study included masked assessments by two independent observers, use of a standardized premature infant pain scale to characterize the pain response to mydriatics, and consideration of the manner in which the eyelids are manipulated during drop administration. The study also has important limitations. Although the study was sufficiently powered (87%) to detect a mean difference in PIPP score of 3, a much larger sample would be needed to identify the characteristics of infants who are most likely to have a clinically significant pain response to mydriatics. We did not study the duration of the pain response, and we did not consider the potential for habituation or sensitization of the pain response to mydriatics, as all subjects were observed with the first set of mydriatic eye drops (3 sets are commonly given) and at their first eye exam (serial examinations are performed). Focusing upon the first administration was felt to provide the “purest” measure of pain response. Duration, habituation and sensitization may all influence the need for comfort measures.

Mydriatic eye drops appear to cause a clinically significant pain response in approximately one third of premature infants. Further investigation may help to predict which infants are at the greatest risk and which comfort measures are most effective in preventing this pain response. Until specific predictive factors are defined, we recommend non-pharmacologic comfort measures be used routinely for infants receiving dilating eye drops in preparation for retinal examinations. The most effective approach may be to establish both the use of comfort measures and minimization of eyelid manipulation as standards of care in the NICU. Such measures are generally neither costly nor time consuming, may help reduce pain in a significant proportion of infants, and can be continued through and reduce the discomfort of the eye exams themselves.

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ABBREVIATIONS

NICU	Neonatal intensive care unit
PIPP	Premature Infant Pain Profile
ROP	Retinopathy of Prematurity

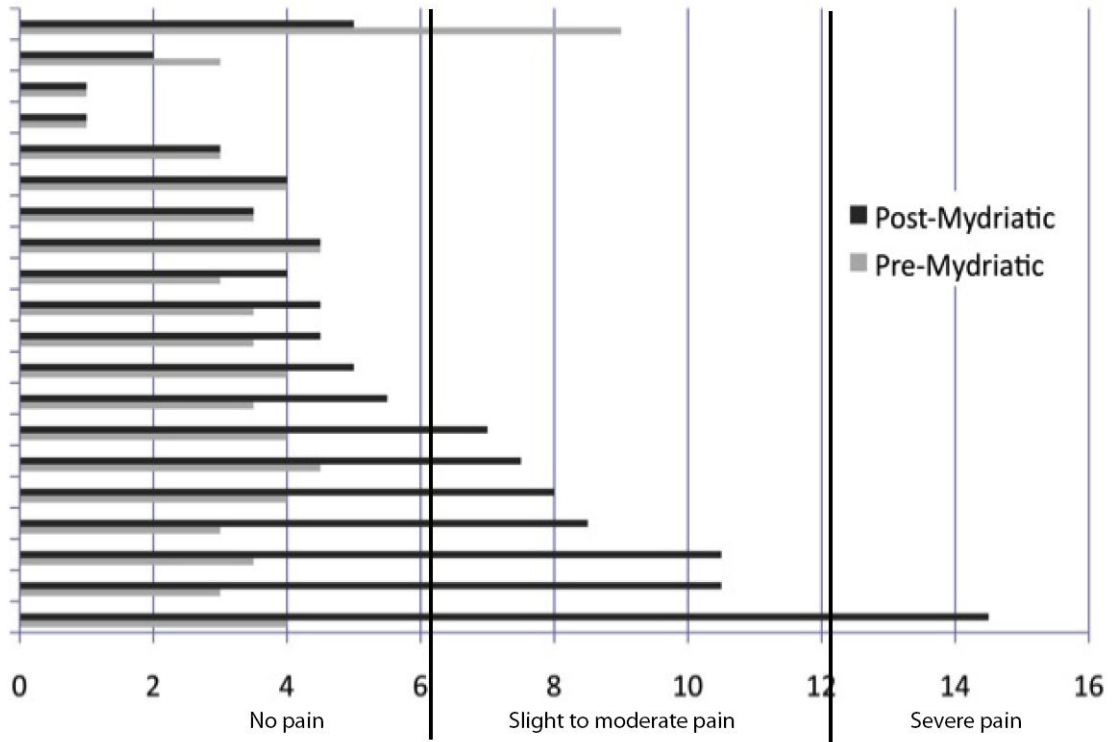


Figure 1.
Pre-mydriatic and post-mydriatic PIPP scores in 20 premature infants.

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Table 1

Characteristics of 20 premature infants assessed for their pain response to mydriatic eye drop administration. SD, standard deviation.

Characteristic	n (%)
Gender	
Male	12 (60)
Female	8 (40)
Race	
African American	9 (45)
Caucasian	11 (55)
Other	1 (10)
Gestational age at birth, weeks	
Mean (SD)	28 4/7 (2.8)
Median (range)	29 (23 - 32 weeks)
Birth weight, g	
Mean (SD)	1080 (347)
Median (range)	1035 (500 – 1835)
Medical history	
Prior intubation	11 (55)
Prior inotropic support	2 (10)
Necrotizing enterocolitis	1 (5)
Sepsis	8 (40)
Intraventricular hemorrhage	
Grade 1	5 (25)
Grade 2	2 (10)
Ventilatory support at time of exam	
None (room air)	11 (55)
Nasal cannula	4 (20)
CPAP	5 (25)
Feeding status at time of exam	
Full feed	20 (100)
Inotropic support at time of exam	
	0
Sedating or pain medications in 48 hours preceding exam	
	0