Pupil Dilatation after Single and Triple Doses of Mydriatic Agent in Preterm Infants

Achara Punyawattanaporn MD*,
Supaporn Tengtrisorn MD*, Pasuree Sangsupawanich MD**

** Department of Ophthalmology, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand*
*** Department of Pediatrics, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand*

Objective: *To compare the pupillary response to a single drop and three drops of a combination of eye drops (0.2% cyclopentolate and 1.0% phenylephrine) in preterm infants.*
Design: *Prospective comparative study.*
Material and Method: *Preterm infants scheduled to undergo their first retinopathy of prematurity (ROP) screening in the Neonatal Intensive Care Unit, Songklanagarind Hospital, between 1 August 2007 and 30 August 2008, were enrolled in the present study. An eyelid speculum was placed after the topical anesthetic, 0.5% tetracaine, application to measure the baseline horizontal pupil diameter with a Vernier caliper. Then each eye was randomized to either receive a drop of mixture of 0.2% cyclopentolate and 1.0% phenylephrine single dose for group A, or triple doses of 10-minute interval for group B. The pupil diameter was measured at 45 and 60 minutes after instillation and a fundus examination was performed afterward.*
Results: *Seventy preterm infants, 45 males and 25 females, were included in the present study. The mean gestational age was 30.49 $\pm$ 2.34 weeks (range of 24-36 weeks) and the mean birth weight was 1,368.00 $\pm$ 438.99 grams (range of 640-2,850 grams). At baseline, the mean pupil diameter was 2.18 $\pm$ 0.44 mm in group A and 2.19 $\pm$ 0.44 mm in group B ($p = 0.90$). The mean pupil diameter at 45 minutes after instillation was 5.50 $\pm$ 0.80 mm in group A and 6.02 $\pm$ 0.56 mm in group B ($p < 0.01$). At 60 minutes after instillation, the mean pupil diameter was 6.13 $\pm$ 0.82 mm in group A and 6.77 $\pm$ 0.41 mm in group B ($p < 0.01$).*
Conclusion: *The pupil size of preterm infants was significantly larger after three drops of the eye drop mixture (0.2% cyclopentolate and 1.0% phenylephrine) than after a single drop. However, a dilated pupil diameter $\geq$ 6 mm was adequate for the peripheral retina examination.*

Keywords: *Premature infant, Retinopathy of prematurity, ROP, Mydriatic*

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Retinopathy of prematurity (ROP) is a disease that affects the immature vasculature in the eyes of premature babies. It may become aggressive with new blood vessel formation (neovascularization) and progress to retinal detachment and blindness. As smaller and younger babies are surviving, the incidence of ROP has increased.

For a complete eye examination in preterm infants, a dilated fundus examination is considered essential for diagnosing and treating. A well-dilated pupil enables proper examination of the peripheral retina to allow diagnosis and staging of ROP[1]. Early detection and management reduces the risk of severe visual loss.

During routine screening for ROP in the Neonatal Intensive Care Unit of Songklanagarind Hospital, pupils are dilated with an eye drop combination (0.2% cyclopentolate and 1.0% phenylephrine) by administering three times of one drop every 10 minutes. Mydriatic agent in preterm infants is associated with systemic side effects. Cyclopentolate is a synthetic tertiary amine antimuscarinic agent that competitively blocks the action of acetylcholine at muscarinic receptors in the iris sphincter and ciliary muscle,

Correspondence to: Tengtrisorn S, Department of Ophthalmology, Faculty of Medicine, Prince of Songkla University, Songkla 90110, Thailand. Phone: 074-451-381, Fax: 074-429-619, E-mail: tsupapor@medicine.psu.ac.th

producing mydriasis and cycloplegia. Phenylephrine is a relatively pure α_1-adrenoceptor agonist, which induces mydrisis by stimulating the iris dilator muscle receptors. The degree of mydrisis is affected by the iris color. Darker eyes are more difficult to dilate than lighter eyes. Cyclopentolate and phenylephrine may cause side effects such as fever, tachycardia, elevated blood pressure, apnea, delayed gastric emptying, and may precipitate to an intraventricular hemorrhage[2,3]. Prior treatment with topical anesthetic agents also enhances the penetration of mydriatic drugs, an effect that may be related to changes in the epithelial barrier after anesthetic application[4].

The 0.2% cyclopentolate and 1.0% phenylephrine eye drop combination use should be minimized in preterm infants. This prospective comparative study compares the pupillary response to a single drop and three drops of the eye drop combination (0.2% cyclopentolate and 1.0% phenylephrine) in preterm infants. The results may be used for routine ROP screening.

Material and Method

Preterm infants scheduled to undergo their first ROP screening in the Neonatal Intensive Care Unit at Songklanagarind Hospital, from August 1, 2007 to August 30, 2008 were enrolled in the present study. The infants, who had congenital ocular anomalies such as coloboma or aniridia, were on medication that might influence pupil diameter such as atropine, and had previous surgery or laser treatment were excluded. The eyelid speculum was placed after the topical anesthetic, 0.5% tetracaine. The baseline horizontal pupil diameter was measured with a Vernier caliper with a reading accuracy of 0.02 mm under the maximum illumination of an indirect ophthalmoscope. Then each eye was randomized to either receive a single drop of the eye drop mixture (0.2% cyclopentolate and 1.0% phenylephrine) for group A or three times of one drop every 10 minutes for group B. The eye was opened 30 seconds after instillation and excess fluid was wiped off the cheek immediately after instillation to prevent absorption through the skin and the nasolacrimal system was occluded for 2 minutes after instillation[5]. The heart rate, systolic, diastolic, and mean blood pressures, as well as other side effects were observed by the nursing staff. The pupil diameter was measured at 45 and 60 minutes after instillation. The fundus examination was performed using the indirect ophthalmoscopy after the measurement of pupil size. If peripheral retina could not be evaluated, repeat mydriatic agents to make the diagnosis and management of ROP possible. The ROP classification is based on the International Classification of Retinopathy of Prematurity (ICROP)[6].

Statistical analysis

The mean pupil sizes were compared between the two groups using the Wilcoxon rank sum test. A p-value of < 0.05 was considered significant.

Results

Seventy preterm infants, 45 males and 25 females, were included in the present study. The mean gestational age was 30.49 ± 2.34 weeks (range of 24-36 weeks), the mean birth weight was $1,368.00 \pm 438.99$ grams (range of 640-2,850 grams) and the mean age was 40.64 ± 21.29 days, as in Table 1.

At baseline, the mean pupil diameter was 2.18 ± 0.44 mm in group A and 2.19 ± 0.44 mm in group B ($p = 0.90$). The mean pupil diameter at 45 minutes after instillation was 5.50 ± 0.80 mm in group A and 6.02 ± 0.56 mm in group B ($p < 0.01$). At 60 minutes after instillation, the mean pupil diameter was 6.13 ± 0.82 mm in group A and 6.77 ± 0.41 mm in group B ($p < 0.01$), as in Table 2.

The mean pupillary diameter was statistically significant larger in group B at 45 and 60 minutes after instillation of mydriatic agents in the complete vascular and prethreshold groups. However, in severe ROP groups could not be compared due to their small sample size, as demonstrated in Table 3-5.

One preterm infant, with a previous history of prematurity, experienced apnea during the mydriatic agent instillation. Other side effects were not found. A pupillary diameter, smaller than 6 mm, was observed in 15/70 (21.4%) eyes in group A, and 1/70 (1.4%) eye in group B. The peripheral retina could not be fully evaluated if the pupillary diameter was smaller than 6mm.

Discussion

Three drops of the eye drop combination (0.2% cyclopentolate and 1.0% phenylephrine) produced larger pupil size than a single drop but both groups had a mean pupillary diameter at 60 minutes larger than 6 mm, and the subgroup analysis of the retinal findings also showed that the pupillary size of preterm infants was larger after three drops.

The standard operating procedure of Songklanagarind Hospital in routine ROP screening is using the eye drop combination (0.2% cyclopentolate

Table 1. Demographic data

Characteristics	Number (%)
Sex	
Male	45 (64.29)
Female	25 (35.71)
Age (days) (mean ± SD)	40.64 ± 21.29
Gestational age (weeks)	
24-30	33 (47.14)
31-33	33 (47.14)
34-36	4 (5.72)
Birth weight (grams)	
501-1,000	15 (21.45)
1,001-1,500	35 (50.00)
1,501-2,000	13 (18.55)
> 2,000	7 (10.00)

Table 2. Comparison of pupillary diameter at baseline, 45 and 60 minutes after instillation of mydriatic agents

Time	Pupillary diameter (mm)		
	Group A	Group B	p-value
Baseline			
Mean ± SD	2.18 ± 0.44	2.19 ± 0.44	0.90
25 percentile	2.00	2.00	
50 percentile	2.20	2.20	
75 percentile	2.50	2.50	
45 minutes			
Mean ± SD	5.50 ± 0.80	6.02 ± 0.56	<0.01
25 percentile	5.25	5.90	
50 percentile	5.80	6.10	
75 percentile	6.00	6.30	
60 minutes			
Mean ± SD	6.13 ± 0.82	6.77 ± 0.41	<0.01
25 percentile	6.00	6.50	
50 percentile	6.28	6.85	
75 percentile	6.70	7.00	

Table 3. The results of fundus examination

Finding	Number of eyes (%)	
	Group A	Group B
Normal	1 (1.43)	1 (1.43)
Incomplete vascular	55 (78.57)	55 (78.57)
Prethreshold	9 (12.8)	9 (12.86)
Threshold	4 (5.71)	5 (7.14)
Stage IV	1 (1.43)	0 (0)
Total	70	70

Table 4. Pupillary diameter (mm) at 45 minutes after instillation of mydriatic agents and retinal findings

Findings	Pupillary diameter (mm) at 45 minutes		
	Group A	Group B	p-value
Normal	5.30	6.80	NA
Incomplete vascular	5.66 ± 0.73	6.13 ± 0.40	<0.01
Prethreshold	5.32 ± 0.65	6.00 ± 0.60	<0.01
Threshold	4.08 ± 0.10	4.80 ± 0.71	NA
Stage IV	4.00	-	NA

Table 5. Pupillary diameter (mm) at 60 minutes after instillation of mydriatic agents and retinal findings

Findings	Pupillary diameter (mm) at 60 minutes		
	Group A	Group B	p-value
Normal	6.00	7.30	NA
Incomplete vascular	6.30 ± 0.66	6.84 ± 0.36	<0.01
Prethreshold	6.11 ± 0.61	6.85 ± 0.51	<0.01
Threshold	4.28 ± 0.21	6.28 ± 0.26	NA
Stage IV	4.20	-	NA

and 1.0% phenylephrine). Chew et al[7] studied the mydriatic regimen that provides optimal dilation of the pupil with minimal systemic side effects for screening of retinopathy of prematurity. The results revealed that the prepared combination of cyclopentolate 0.2% and phenylephrine 1% appears to be the mydriatic of choice for preterm infants with dark irides as it provided adequate pupillary dilation with the least systemic side effects. To the authors' knowledge, no previous study to compare the pupillary response to a single drop and three drops of the eye drop combination (0.2% cyclopentolate and 1.0% phenylephrine) or any other regimen in preterm infants has been conducted. The results of the present study are different from those of other studies in childhood and adult[8-10] because the age group, drugs, method of instillation and diseases, which effect the pupil size, were different.

The present study compared the pupillary response between both eyes in the same infant. The systemic side effects were reduced by punctal occlusion and the wiping away of excess fluid from the

periocular area. However, many studies have reported systemic side effects such as fever, tachycardia, elevated blood pressure, apnea, delayed gastric emptying and intraventricular hemorrhage[2,3,11,12]. The present study found one infant had apnea during the instillation of the mydriatic agents. This infant had a previous history of apnea. The present study could not compare the side effects between the two groups because both groups studied the same infants.

The present study enrolled a large number of preterm infants compared with previous studies, however, the number of those with the threshold ROP and stage IV ROP subgroups was rather small. From this result, the authors suggest that preterm infants who undergo ROP screening to dilate with a single drop first and wait for 60 min. If the pupillary size is > 6 mm the authors will proceed with fundus examination. If the pupillary size is < 6 mm, ROP may be suspected and more drops are required.

In conclusion, the pupillary size of preterm infants was significantly larger after three drops of the eye drop combination (0.2% cyclopentolate and 1.0% phenylephrine) than after a single drop. However, a dilated pupil diameter of > 6 mm was adequate for examination of the peripheral retina.

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References

1. Parisi ML, Scheiman M, Coulter RS. Comparison of the effectiveness of a nondilated versus dilated fundus examination in the pediatric population. J Am Optom Assoc 1996; 67: 266-72.
2. Zimmerman CF, Hogan RN, Le TD. Mydriatic and cycloplegic drugs. In: Zimmerman TJ, Koonere KS, Fechtner RD, Sharir M, editors. Textbook of ocular pharmacology. Philadelphia: Lippincott-Raven; 1997: 807-26.
3. Blansett DK. Dilatation of the pupil. In: Bartlett JD, Jaanus SD, editors. Clinical ocular pharmaco- logy. 4th ed. Woburn: Butterworth-Heinemann; 2001: 405-23.
4. Apt L, Henrick A. Pupillary dilatation with single eyedrop mydriatic combinations. Am J Ophthalmol 1980; 89: 553-9.
5. Nelson LB. Retinopathy of prematurity. In: Nelson LB, Harley RD, editors. Harley's pediatric ophthalmology. 4th ed. Philadelphia: WB Saunders; 1998: 60-81.
6. The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. Arch Ophthalmol 1984; 102: 1130-4.
7. Chew C, Rahman RA, Shafie SM, Mohamad Z. Comparison of mydriatic regimens used in screening for retinopathy of prematurity in preterm infants with dark irides. J Pediatr Ophthalmol Strabismus 2005; 42: 166-73.
8. Siderov J, Nurse S. The mydriatic effect of multiple doses of tropicamide. Optom Vis Sci 2005; 82: 955-8.
9. Ratanapakorn T, Yospaiboon Y, Chaisrisawadsuk N. Single dose of 1% tropicamide and 10% phenylephrine for pupil dilation. J Med Assoc Thai 2006; 89: 1934-9.
10. Hug T, Olitsky S. Dilation efficacy: is 1% cyclopentolate enough? Optometry 2007; 78: 119-21.
11. Rush R, Rush S, Nicolau J, Chapman K, Naqvi M. Systemic manifestations in response to mydriasis and physical examination during screening for retinopathy of prematurity. Retina 2004; 24: 242-5.
12. Bonthala S, Sparks JW, Musgrove KH, Berseth CL. Mydriatics slow gastric emptying in preterm infants. J Pediatr 2000; 137: 327-30.

การขยายรูม่านตาด้วยการหยอดยาครั้งเดียวและสามครั้งในทารกที่เกิดก่อนกำหนด

อัจฉรา ปัญญาวัฒนาภรณ์, สุภาภรณ์ เต็งไตรสรณ์, ภาสุรี แสงศุภวานิช

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบผลการขยายรูม่านตาด้วยการหยอดยาผสม 0.2% cyclopentolate และ 1.0% phenylephrine ครั้งเดียวและสามครั้งในการตรวจจอตาในทารกที่เกิดก่อนกำหนด การออกแบบการศึกษาเปรียบเทียบแบบมุ่งหน้า*

วัสดุและวิธีการ: *เก็บข้อมูลในทารกเกิดก่อนกำหนดที่กุมารแพทย์ส่งตรวจคัดกรองโรคจอตาผิดปกติจากหออภิบาลเด็กอ่อนโรงพยาบาลสงขลานครินทร์ ตั้งแต่วันที่ 1 สิงหาคม พ.ศ. 2550 ถึง 30 สิงหาคม พ.ศ. 2551 โดยหยอดยา 0.5% tetracaine แล้วใส่ eye speculum เพื่อวัดขนาดรูม่านตาแนวนอนโดยใช้ vernier caliper แล้วสุ่มเลือกตาหนึ่งข้างหยอดยาผสม 0.2% cyclopentolate และ 1.0% phenylephrine ครั้งเดียว (กลุ่ม A) และอีกข้างหยอดสามครั้ง (กลุ่ม B) แต่ละครั้งห่างกัน 10 นาที โดยเปิดตาค้างไว้ 30 วินาที กดหัวตานาน 2 นาที จากนั้นวัดขนาดของรูม่านตาที่ 45 และ 60 นาทีแล้วจึงตรวจจอตา*

ผลการศึกษา: *ผู้ป่วยที่ศึกษามีทั้งหมด 70 คน เพศชาย 45 คน เพศหญิง 25 คน อายุครรภ์เฉลี่ย 30.49 $\pm$ 2.34 สัปดาห์ (range 24-36 สัปดาห์) น้ำหนักแรกเกิดเฉลี่ย 1368.00 $\pm$ 438.99 กรัม (range 640-2850 กรัม) ก่อนการหยอดยาขนาดรูม่านตาเฉลี่ยในกลุ่ม A เท่ากับ 2.18 $\pm$ 0.44 มม. ขนาดม่านตาในกลุ่ม B เท่ากับ 2.19 $\pm$ 0.44 มม. ($p = 0.90$) หลังหยอดยา 45 นาที ขนาดรูม่านตาเฉลี่ยในกลุ่ม A เท่ากับ 5.50 $\pm$ 0.80 มม. ม่านตาในกลุ่ม B เท่ากับ 6.02 $\pm$ 0.56 มม. ($p < 0.01$) หลังหยอดยา 60 นาทีขนาดรูม่านตาเฉลี่ยในกลุ่ม A เท่ากับ 6.13 $\pm$ 0.82 มม. ขนาดม่านตาในกลุ่ม B เท่ากับ 6.77 $\pm$ 0.41 มม. ($p < 0.01$)*

สรุป: *การหยอดยาผสม 0.2% cyclopentolate และ 1.0% phenylephrine ครั้งเดียว ขนาดรูม่านตามีความแตกต่างกับการหยอดสามซรั้งอย่างมีนัยสำขัญทางสถิติ อย่างไรก็ตามขนาดรูม่านตาโดยเฉลี่ยของทั้งสองกลุ่มมากกว่า 6 มม. ที่เวลา 60 นาทีหลังหยอดยาซึ่งเพียงพอในการตรวจคัดกรองโรฆจอตาผิดปกติในทารกเกิดก่อนกำหนด*