Comparison of the Effectiveness of Mydriasis by Two Instillation Methods of Combined 0.75% Tropicamide and 2.5% Phenylephrine Eye Drop in Preterm Infants

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Objective: *To compare the effectiveness and safety of two instillation methods of combined 0.75% tropicamide and 2.5% phenylephrine at 0, 5 minutes (min) with the same combined regimen at 0,30 minutes in preterm infants.*
Material and Method: *A prospective, cross-over, randomized controlled trial was performed to compare 0, 5-min instillation (Method A) of combined 0.75% tropicamide and 2.5% phenylephrine with 0, 30-min instillation (Method B) of the same regimen. Forty-two preterm infants scheduled for screening retinopathy of prematurity (ROP) were randomly assigned to two groups. Group 1 was defined as preterms applied by Method A at first examination then by Method B 1-4 weeks apart whereas vice versa in Group 2. Pupil size, heart rate (HR), systolic and diastolic blood pressure (SBP, DBP) were recorded before and after eye-drop instillation.*
Results: *Mean time to 7-mm pupil size was no statistically significant difference between the two methods (Method A 46.47 min, Method B 46.58 min; p = 0.894). Method B has mean longer time to maintain 7-mm pupil size than Method A (Method A 67.67 min, Method B 75.33 min); but not statistically significant different (p = 0.323). HR, SBP and DBP were not significant change between the two methods.*
Conclusion: *Both instillation methods produced consistently sufficient mydriasis and safety for evaluation peripheral fundus. Method B has slight longer mydriatic effect than Method A; thus giving more time to evaluate infant's eye for ophthalmologists.*

Keywords: *Mydriasis, Pupillary dilation, Tropicamide, Phenylephrine, Retinopathy of prematurity (ROP), Preterm infants*

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Retinopathy of prematurity (ROP) is a disorder of the developing retina of low birth weight preterm infants that potentially results in functional or complete blindness. Screening and subsequent examination of premature infants by an experienced ophthalmologist is mandatory because of the sequential nature of ROP progression and the proven benefits of timely treatment in reducing the risk of visual loss in ETROP study[1,2]. Since 2000, pediatricians and ophthalmologists revised the criteria for screening examination of premature infants for ROP in Siriraj Hospital[3]. Adequate mydriasis, however, is necessary to allow proper evaluation and management of the retina in decreasing the incidence of poor visual outcome in premature infants.

Although mydriatic agents are generally required in dilated fundus examination to provide adequate assessment, these agents produce insufficient mydriasis as well as systemic side effects in premature infants[4-8]. Phenylephrine 2.5-10% can cause cardiovascular effects including significant hypertension[9-11] and may precipitate intracranial hemorrhage[12]. Previous studies[13,14] showed effectiveness and safety of a single combination eye drop of 0.5% tropicamide and 2.5% phenylephrine in premature infants. Therefore, a combination of mydriasis is prerequisite to obtain adequate mydriasis at a minimum risk of systemic side effects.

To date, no prior study has reported onset

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and duration of maximum action as well as instillation in different time of this combination regimen. This prospective, randomized, controlled trial compares the effectiveness and safety of 0.75% tropicamide and 2.5% phenylephrine at 0, 5 minutes with same combination regimen at 0, 30 minutes in preterm infants.

Material and Method

Forty-two premature infants scheduled for routine screening ophthalmoscopy (for retinopathy of prematurity) were enrolled in the present study. Eligible criteria were premature infants with a birth weight less than 1,501 g and/or gestational age less than 33 weeks. Premature infants with congenital anomalies of the iris, cardiovascular diseases with hemodynamic significance and previous dilated fundus examination were excluded from the present study.

A mydriatic eye-drop combination was 0.75% tropicamide and 2.5% phenylephrine. All eligible premature infants were randomly and equally categorized into two groups: group 1-a combined mydriatic eye drop was instilled in each eye by Method A at the first fundus examination then by Method B at the second examination 1-4 weeks later in 21 preterm infants, group 2-the remainder were instilled in each eye by Method B first then by Method A 1-4 weeks apart. Single-drop instillation of combined mydriatic eye-drop at 0 and 5 minutes (min) was defined as Method A whereas Method B was instillation of the eye-drop at 0 and 30 min. To minimize transcutaneous absorption, any excess fluid was wiped off immediately.

Pupillary diameter was measured with a pupil gauge held almost touching the cornea before administration of the first drop and then every 10 min after the first drop until the pupil was dilated fully. To obtain the strength of combined mydriatic eye-drop, the measurement of pupil size was carried out until pupil diameter was less than 7 mm. The examination was performed in ambient light. Three investigators completed all measurements.

Heart rate (HR) and blood pressure (BP) were monitored using Dynamap 1846 Vital Signs Monitor (Critikon Inc, Tampa, FL). A neonatal cuff was placed on the infant's calf without an intravenous line and left in place throughout the entire measurement period to ensure uniformity for each measurement. Measurements were made immediately prior to instillation of the drops to determine baseline and cardiovascular stability and then at 10-minute intervals during pupillary measurement. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were recorded by three investigators.

After acquiring pupil size, BP and HR, fundus examinations were performed and the stage of any retinopathy of prematurity was noted. All mydriatic examinations were medically indicated; no unnecessary examinations were done. The data were analyzed using a paired t-test and Chi-square test p-value of < 0.05 was set for statistically significant. The present study was approved by Siriraj Ethics Committee, Mahidol University. All parents of the infants studied provided written consent to the screening and follow-up assessments.

Results

Table 1 shows demographic data of the patients. Forty-two infants comprised the study population. The sex ratio was 18 males to 24 females. Mean gestational age was 30.5 weeks (range; 25-38 wks) and mean birth weight was 1,241.9 g (range; 590-1,940 g). Mean Apgar score at 1, 5 and 10 min were 5.35, 7.77 and 8.21 respectively.

Table 1. Clinical characteristics of the patients

Variables	Value (range)
Gender male:female (%)	18:24 (42.9:57.1)
GA (wk) mean $\pm$ SD	30.50 $\pm$ 3.0 (25-38)
Birth weight(g) mean $\pm$ SD	1,241.90 $\pm$ 301.3 (590-1,940)
Postconceptional age (wk) mean $\pm$ SD	31.07 $\pm$ 2.7 (27-38)
Body weight at examination (g) mean $\pm$ SD	1,620 $\pm$ 399.6 (770-2,530)
Apgar score	
1 min	5.35 $\pm$ 2.9 (1-10)
5 min	7.77 $\pm$ 2.1 (3-10)
10 min	8.21 $\pm$ 1.9 (4-10)

GA = Gestational age

Mydriatic effect

Table 2 and Fig. 1, 2 show the pupillary dilating effect of both methods. At baseline, the mean initial diameter of the pupils was slightly larger in Method A than in Method B. In Method A, mean time of the pupillary diameter of reaching a mean of 7 mm for both eyes is 46.47 min (± 14.54 SD) whereas mean time of pupillary diameter to 7 mm is 46.58 min in Method B, which is not a statistically, significant difference (p = 0.894), (95%CI 41.583, 51.358). Mean maximum pupillary dilatation in both methods was achieved in 70 mins (Method A: 7.59 mm, Method B: 7.81 mm). Mean time to maintain 7 mm of pupillary diameter in Method A and B is 64.69 min and 72.29 min respectively, which is not a statistically significant difference between the two methods (p = 0.323), (95%CI -23.254, 7.921) (Table 3).

Systemic effect

Comparisons of mean HR, SBP and DBP between the two methods are demonstrated in Table 4 and Fig. 3, 4. At 60 min after the first drop, mean HR, SBP and DBP in Method A and B were 151 and 153 beats/min, 68 and 69 mmHg, 38 and 36 mmHg respectively. There was no statistically significant difference in SBP, DBP and HR at 60 min between the two methods (HR; p = 0.467, SBP; p = 0.943, DBP; p = 0.213). Table 5 summarizes mean changes in SBP, DBP and HR of the two methods. There was no statistically significant increase in SBP and DBP over baseline but slightly decreases in HR from baseline, which had a mean decrease change in Method A and B of 6 and 4 beats/min, respectively. However, comparison of the

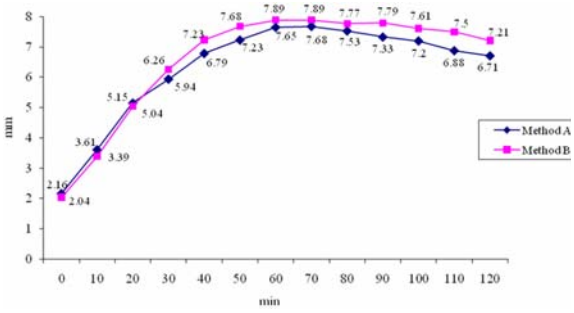


Fig. 1 Mean pupil size of right eye over time of Method A and B

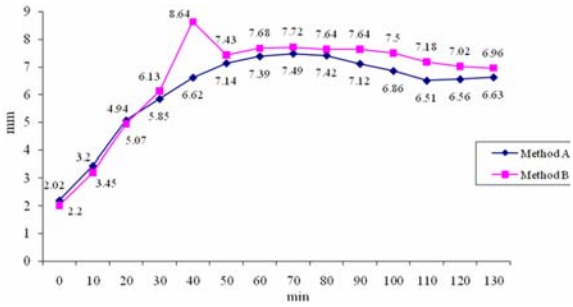


Fig. 2 Mean pupil size of left eye over time of Method A and B

Table 2. Mean pupillary diameter of both eyes response to Method A and B

	Mean pupil size (mm)			
	Right eye		Left eye	
	Method A	Method B	Method A	Method B
0 min	2.16	2.04	2.20	2.02
10 min	3.61	3.39	3.45	3.20
20 min	5.15	5.04	5.07	4.94
30 min	5.94	6.26	5.85	6.13
40 min	6.79	7.23	6.62	8.64
50 min	7.23	7.68	7.14	7.43
60 min	7.65	7.89	7.39	7.68
70 min	7.68	7.89	7.49	7.72
80 min	7.53	7.77	7.42	7.64
90 min	7.33	7.79	7.12	7.64
100 min	7.20	7.61	6.86	7.50
110 min	6.88	7.50	6.51	7.18
120 min	6.71	7.21	6.56	7.02

Table 3. Mean time to reach and maintain 7-mm pupil size of Method A and B

	Method A	Method B	p-value
Mean time to 7-mm pupil size (min) ± SD	46.47 ± 14.54	46.58 ± 15.82	0.894
Mean time to maintain 7-mm pupil size (min) ± SD	64.69 ± 30.27	72.29 ± 36.71	0.323

Table 4. Mean heart rate, systolic and diastolic pressure response to Method A and B

	HR (beat/min)		SBP (mmHg)		DBP (mmHg)	
	Method A	Method B	Method A	Method B	Method A	Method B
0 min	157	157	68	68	37	37
10 min	156	153	68	67	38	37
20 min	156	152	69	69	38	36
30 min	152	154	68	69	36	37
40 min	156	151	67	70	39	36
50 min	150	154	69	68	37	37
60 min	151	153	68	69	38	36
70 min	153	152	70	70	37	37
80 min	155	153	69	70	39	39
90 min	152	154	70	70	38	39
100 min	150	151	67	72	37	40
110 min	154	152	68	71	38	38
120 min	155	153	68	70	38	38

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure

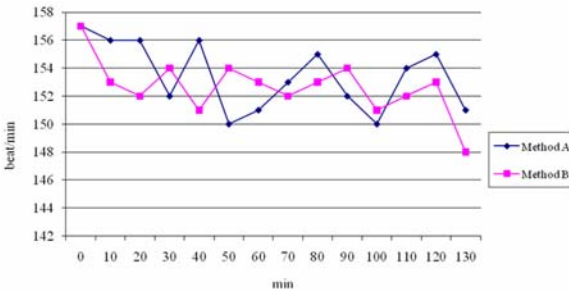
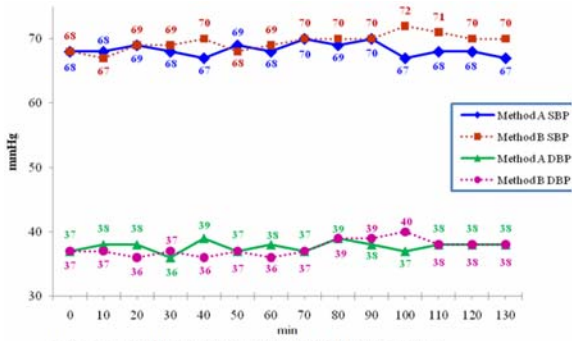


Fig. 3 Mean heart rate over time of Method A and B



SBP = systolic blood pressure, DBP = diastolic blood pressure

Fig. 4 Mean systolic and diastolic blood pressure over time of Method A and B

mean changes in SBP, DBP and HR at 60 min did not reveal any significant differences between the two methods. In both methods, increased SBP and DBP were followed by a slight reduction of all BP means below baseline values. This rebound effect was seen 20 min in SBP and 40 min in DBP after the first eye drop. No infants in the present study have shown hyperexcitation or otherwise striking behavioral or neurological changes.

Discussion

Both instillation methods produced consistently adequate mydriasis. The Method A produced mydriasis was not statistically different from that produced by the Method B, although the latter method used two instillations 30 mins apart. Neither instillation methods produced any rise in systolic or diastolic blood pressure and heart rate over baseline. The present study has a relatively large sample size (42 infants); each group was crossed over 1 week apart to obtain both instillation methods for avoiding bias.

Table 5. Mean change in heart rate, systolic and diastolic pressure response to Method A and B

	HR (beat/min)		SBP (mmHg)		DBP (mmHg)	
	Method A	Method B	Method A	Method B	Method A	Method B
10 min	-1	-4	0	-1	1	0
20 min	-1	-5	1	1	1	-1
30 min	-5	-3	0	1	-1	0
40 min	-1	-6	-1	2	2	-1
50 min	-7	-3	1	0	0	0
60 min	-6	-4	0	1	1	-1
70 min	-4	-5	2	2	0	0
80 min	-2	-4	1	2	2	2
90 min	-5	-3	2	2	1	2
100 min	-7	-6	-1	4	0	3
110 min	-3	-5	0	3	1	1
120 min	-2	-4	0	2	1	1

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure

To obtain adequate assessment of the peripheral fundus, some ophthalmologists recommend a pupillary diameter of at least 7 mm[15] but others have found that significantly less dilatation is adequate[9,16,17]. For optimal dilation in preterm infants, solutions containing both parasympatholytic (tropicamide) and sympathomimetic (phenylephrine) drugs are essential[16,18]. This combination acts synergistically on both iris dilator and sphincter muscles to produce maximal mydriasis that resists intense light[19]. Theoretically, combination of tropicamide and phenyephrine eye drops had onset of dilation at 30-60 min. In the present studies, mean time to achieve 7-mm pupillary diameter was similar to other study[20,21] that is consistent with theory in both methods (Method A: 46.47, Method B: 46.58). The pupillary dilatation was sufficient to evaluate the peripheral retina in most previous studies[9,18] although combination of mydriatic agents in each one was not quite different. Interestingly, estimated onset and duration to maintain 7-mm pupillary diameter of this combination eye drop were established in the present study. Even though there was no significant difference in both variables of the two methods, these numbers gave benefits to both ophthalmologists and Newborn Intensive Care Unit (NICU) nurses. As the estimated time to maintain 7-mm pupillary diameter shown in the present study, NICU nurses can predict the time for examining the fundus of premature infants. Thus, there will have more time for both ophthalmologists and nurses during awaiting the period.

Mean time to maintain 7-mm pupil size in Method B is longer than Method A but not statistically significant (p = 0.323). Even though this parameter is not of statistically significant difference, 95% CI is rather broad (-23.254 to 7.921) and involves a point of clinical importance that indicates the sample size in the present study is too small. This means p-value of this parameter will be significant if more premature infants are included in the present study.

Since 1956, McReynolds et al[22] first reported on reactive hypertension after application of 10% phenylephrine as a mydriatic in an adult, Borroneo-McGrail et al[23] confirmed a significant blood pressure rise in 1-month-old premature infants applied with 10% phenylephrine eye drop. In the present study, there was no statistically significant change over baseline in mean SBP and DBP at 60 minutes between two the methods. Also, mean change in SBP and DBP was small. This finding is consistent with previous studies. Caputo and Schnitzer[18] reported no statistical pressure rise in 12 neonates. Likewise, Merrit and Kraybill[24] also did not find any statistical pressure increase after triple instillation in 52 heavier babies (mean BW 1,569 g). Others[13,25] also have reported good results with a single instillation of combined 0.5% tropicamide and 2.5% phenylephrine followed by tropicamide 20 min later. In contrast to the findings of Rosales et al[9] and Isenberg and Everett[17] who found a significant BP rise when using 2.5% phenylephrine.

Although mean SBP and DBP at 100 min in Method B showed a peak rise but was not clinically

significant, none became hypertensive. None of the effects seen in both methods was significantly different from baseline values. A possible explanation that a peak rise of BP at 100 min in Method B is the last drop applied at 30 min after the first drop lasts longer in duration than in Method A.

In the present study, both methods receiving phenylephrine demonstrated a small deceleration of HR below baseline. There was no significant difference in the deceleration between the two methods. The mean deceleration of HR at 60 min was 6 beats/min in Method A and 4 beats/min in Method B; this difference is too small to be clinically significant. Isenberg et al[21] reported no elevation of HR but slight reduction of BP after 0.5% cyclopentolate alone; 0.5% cyclopentolate plus 0.5% tropicamide and a combination of 0.2% cyclopentolate and 1% phenylephrine.

To achieve optimal assessment and minimize systemic side effect, the authors' approach involved reducing the concentration of combination eye drop as well as the number of instillations. Bolt et al[13] recommended two times of combined 2.5% phenylephrine and 0.5% tropicamide, which is nearly the same concentration as in the present study to acquire a sufficient diagnostic mydriasis without systemic side effects in preterm infants. Because the eye drops were applied to premature infants by NICU nurses, attempt to reduce the number of instillations was created. The instillation method, however, was variably different among NICU nurses. To integrate various instillation methods in Siriraj Hospital, two common administrations were selected to compare the effectiveness and safety.

In summary, two instillation methods of combined 0.75% tropicamide and 2.5% phenylephrine is a sufficient mydriasis for preterm infants to be screened for retinopathy of prematurity. A 0, 30-min interval method of this combined regimen lasts longer mydriasis than a 0, 5-min interval method. Neither method produced any clinically significant changes in BP or HR.

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Potential conflicts of interest

None.

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การเปรียบเทียบประสิทธิผลของการขยายรูม่านตาระหว่างวิธีหยอดยาผสม 0.75% tropicamide กับ 2.5% phenylephrine 2 วิธี

พิทยา ภมรเวชวรรณ, กัญญา จุฑาสมิต, ปาริชาติ ดำรงรักษ์, สุพรรณา กู้เกียรติกูล, ทัศนีย์ วงศ์เกียรติ์ขจร, โสภาพรรณ เงินฉ่ำ

วัตถุประสงค์*: เพื่อเปรียบเทียบประสิทธิผลและความปลอดภัยของวิธีหยอดยาผสม 0.75% tropicamide กับ 2.5% phenylephrine ที่ 0 และ 5 นาที (วิธี A) กับการหยอดยาผสมสูตรเดียวกันที่ 0 และ 30 นาที (วิธี B) ในทารกเกิดก่อนกำหนด*

วัสดุและวิธีการ*: เป็นการศึกษาไปข้างหน้าแบบสุ่มในทารกเกิดก่อนกำหนด 42 คน ที่จะได้รับการตรวจคัดกรองโรคจอตา เหตุทารกเกิดก่อนกำหนด โดยแบ่งทารกออกเป็น 2 กลุ่ม กลุ่มที่ 1 คือ ทารกเกิดก่อนกำหนดที่ถูกหยอดยาผสมครั้งแรกด้วยวิธี A และ 1-4 สัปดาห์ ต่อมาเป็นครั้งที่สองด้วยวิธี B ส่วนกลุ่มที่ 2 คือทารกเกิดก่อนกำหนดที่ถูกหยอดยาผสมครั้งแรกด้วยวิธี B และ 1-4 สัปดาห์ต่อมาด้วยวิธี A และมีการบันทึกขนาดรูม่านตา อัตราการเต้นของหัวใจ และความดันโลหิต ทั้งก่อนและหลังการหยอดยาขยายรูม่านตา*

ผลการศึกษา*: ระยะเวลาเฉลี่ยที่ใช้ในการขยายขนาดรูม่านตาจนถึง 7 มิลลิเมตรของทั้งวิธี A และ B ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (ค่าเฉลี่ยวิธี A = 46.47 นาที วิธี B = 46.58 นาที) ส่วนวิธี B มีค่าเฉลี่ยของช่วงเวลาที่ขนาดรูม่านตาคงอยู่ถึง 7 มิลลิเมตร นานกว่าวิธี A (ค่าเฉลี่ยวิธี A = 67.67 นาที วิธี B = 75.33 นาที) แต่ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างสองวิธี รวมถึงอัตราการเต้นของหัวใจ และความดันโลหิตก็ไม่มีความแตกต่างกันอย่างมีนัยสำคัญระหว่างสองวิธี*

สรุป*: การหยอดยาผสมทั้ง 2 วิธี มีประสิทธิผลในการขยายขนาดรูม่านตาได้เพียงพอและปลอดภัยในการตรวจจอตา วิธี B มีผลในการคงขนาดรูม่านตา 7 มิลลิเมตร นานกว่าวิธี A เล็กน้อย จึงมีเวลาในการตรวจจอตาสำหรับจักษุแพทย์นานขึ้น*