Comparison of Mydriatic Regimens Used in Screening for Retinopathy of Prematurity in Preterm Infants With Dark Irides

Carmen Chew, MD; Ropilah Abdul Rahman, MD; Suraiya M. Shafie, MD; and Zainal Mohaniad, MD

ABSTRACT

Purpose: To determine the mydriatic regimen that provides optimal dilation of the pupil with minimal systemic side effects for screening of retinopathy of prematurity.

Methods: This cross-sectional, randomized, double-masked clinical trial compared cyclopentolate 1% + phenylephrine 2.5%, tropicamide 1% + phenylephrine 2.5%, and a prepared combination of cyclopentolate 0.2% with phenylephrine 1% for pupillary dilation in preterm infants with dark irides. Thirteen infants were randomized to each regimen. Outcomes measured were pupillary dilation, heart rate, blood pressure, abdominal girth, and intolerance to feeds.

Results: All three mydriatic regimens provided adequate pupillary dilation at 45 minutes, with dilation sustained at 60 minutes. There was a significant increase in mean blood pressure in the cyclopentolate 1% + phenylephrine 2.5% and the tropicamide 1% + phenylephrine 2.5% groups. Although there was no significant change of abdominal girth in any of the three groups, a total of eight patients developed intolerance to feeds; four (50%) of these infants were from the cyclopentolate 1% + phenylephrine 2.5% group.

Conclusion: The prepared combination of cyclopentolate 0.2% + 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.


INTRODUCTION

The primary aim of the ophthalmoscopic examination of preterm infants is to detect any retinal abnormalities associated with retinopathy of prematurity (ROP). A well-dilated pupil enables proper examination of the peripheral retina to allow diagnosis and staging of ROP. Early detection and timely management significantly reduces the risk of severe visual loss.
An ideal mydriatic regimen should provide maximum mydriasis at the lowest possible risk of side effects. Many studies have been conducted to determine the ideal mydriatic regimen for preterm infants. Unfortunately, these studies yielded controversial results concerning the extent of pupillary dilation as well as the cardiovascular side effects in premature infants. Although routine screening for ROP is carried out in all neonatal units in Malaysia, no study has been conducted to determine the safety and efficacy of the various commercially prepared mydriatic agents used. This study was conducted to determine the effectiveness and safety of three commonly used mydriatic agents in preterm infants with dark irides.

The objectives of our study were to compare the amount of pupillary dilation achieved using three different mydriatic regimens. Cardiovascular and gastrointestinal side effects (heart rate; systolic, diastolic, and mean blood pressures; and abdominal distension or intolerance to feeds) of the mydriatic regimens were compared.

**METHODS**

This cross-sectional, randomized, double-masked clinical trial compared three mydriatic regimens used in screening of ROP in preterm infants. Thirty-nine preterm infants who were scheduled to undergo ROP screening in the neonatal intensive care unit, Hospital University Kebangsaan Malaysia, from April 2000 to September 2001 comprised the study population. Infants with any of the following were excluded from the study: congenital ocular anomalies of the iris (coloboma or aniridia); developmental anomalies of the cardiovascular, gastrointestinal, or central nervous system; light irides; dependence on assisted ventilation support or a generally unstable condition; recurrent bouts of vomiting or intolerance to feeds; a medication regimen that might influence heart rate, blood pressure, or the gastrointestinal system (eg, beta-blockers and antiemetics); and ROP with plus disease.

Infants were randomized into three mydriatic regimen groups:

- Group 1 received cyclopentolate 1% + phenylephrine 2.5%,
- Group 2 received tropicamide 1% + phenylephrine 2.5%, and
- Group 3 received a commercial preparation of phenylephrine 1% with cyclopentolate 0.2%.

**Table 1** outlines the mydriatic regimens. The phenylephrine 2.5% (Mydfrin 2.5%, Alcon Laboratories Inc., Fort Worth, TX) and phenylephrine 1% with cyclopentolate 0.2% (Cyclomedrill, Alcon Laboratories Inc.) were supplied in 5-mL bottles, whereas the cyclopentolate 1% (Cyclomydril, Alcon Laboratories Inc.) and tropicamide 1% (Mydriacyl 1%, Alcon Laboratories Inc.) were supplied in 15-mL bottles. For patients in group 3, normal saline was placed into a 15-mL bottle and administered prior to the mydriatic drops. Masking was achieved by removing the original labels of all bottles. Bottles were then color coded by an independent observer. All of the bottles had uniform bottle caps. The investigator and the nurses who administered the eye drops and recorded the systemic parameters were masked to the bottle contents. Coding was revealed only at the end of the study.

Baseline horizontal pupillary diameter was measured with a vernier caliper that allowed a reading accuracy of 0.05 mm under the maximum illumination of a portable indirect ophthalmoscope (Heine Sigma 150). The eyelids were held open by a lid speculum under local anesthesia benoxinate hydrochloride 0.4%. Baseline heart rate and systolic, diastolic, and mean blood pressures then were measured by the nursing staff using Press-Mate, model BP-8800C (Colin Medical Instruments Corp., San Antonio, TX) with a neonatal cuff placed on the infant's calf. The average of three observations at 10 minutes, 5 minutes, and immediately prior to instillation of the first round of eye drops served as the baseline measurement. The blood pressure cuff was
left in place throughout the study. Abdominal girth was measured using a measuring tape with an accuracy of 0.5 cm, at the level of the umbilicus, and measurements were obtained before or 1 hour after feeds.

The first eye drop was instilled from the bigger bottle (tropicamide 1%, cyclopentolate 1%, or normal saline) followed by another drop from the smaller bottle (phenylephrine 2.5% or phenylephrine 1% with cyclopentolate 0.2%) 2 minutes later (Table 1). The second and third rounds of eye drops were instilled after 5 and 10 minutes, respectively. Eye drops were instilled into the inferior fornix, and cutaneous absorption was minimized by wiping away excess fluid from the periocular area.

Heart rate and systolic, diastolic, and mean blood pressures were obtained at 5, 10, 15, 30, 45, and 60 minutes after instillation of the first eye drop. Pupils were examined at 45 and 60 minutes. Abdominal girth was measured at 6, 12, 18, and 24 hours after instillation of eye drops. Any episodes of vomiting or intolerance to feeds within 24 hours of instillation of the first round of eye drops were recorded.

Statistical evaluation of pupillary diameter; heart rate and systolic, diastolic, and mean blood pressures; and abdominal girth was performed using a two-tailed t test, and mean increase in pupillary dilation achieved at 45 and 60 minutes was evaluated using a paired t test. A P value < .05 was considered statistically significant.

RESULTS

Patient Characteristics

Thirty-nine infants were enrolled in the study, with 13 patients in each mydriatic regimen group. There were 24 (61.5%) Malay, 12 (30.8%) Chinese, and 3 (7.7%) Indian patients. The overall mean (±SD) gestational age at birth was 29.4 ± 2.28 weeks. Birth weight for the majority of patients was > 1,000 g (Table 2).

Effectiveness of Mydriatic Regimens on Pupillary Dilation

The pupillary-dilating effect of the mydriatic regimens are compared in Table 3. At baseline, mean initial pupillary diameter was 2.13 ± 0.54 mm for the right eye and 2.13 ± 0.51 mm for the left eye. Pupils were slightly smaller in group 1 at baseline, but this difference was not statistically significant.

At 45 minutes after instillation of the first eye drops, most of the eyes reached a mean pupillary diameter ≥ 6 mm. Mean pupillary diameters for the
TABLE 3
COMPARISON OF PUPILLARY DIAMETER AT BASELINE, 45, AND 60 MINUTES AFTER INSTILLATION OF MYDRIATIC AGENTS

<table>
<thead>
<tr>
<th>Time</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye</td>
<td>1.97 ± 0.59</td>
<td>2.09 ± 0.54</td>
<td>2.33 ± 0.45</td>
<td>.236</td>
</tr>
<tr>
<td>Left eye</td>
<td>2.01 ± 0.61</td>
<td>2.07 ± 0.44</td>
<td>2.31 ± 0.46</td>
<td>.294</td>
</tr>
<tr>
<td>45 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye</td>
<td>6.10 ± 0.57</td>
<td>5.98 ± 0.64</td>
<td>6.01 ± 0.58</td>
<td>.867</td>
</tr>
<tr>
<td>Left eye</td>
<td>6.22 ± 0.55</td>
<td>6.05 ± 0.75</td>
<td>6.04 ± 0.57</td>
<td>.715</td>
</tr>
<tr>
<td>60 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye</td>
<td>6.47 ± 0.51</td>
<td>6.18 ± 0.55</td>
<td>6.34 ± 0.56</td>
<td>.396</td>
</tr>
<tr>
<td>Left eye</td>
<td>6.49 ± 0.48</td>
<td>6.23 ± 0.67</td>
<td>6.17 ± 0.56</td>
<td>.342</td>
</tr>
</tbody>
</table>

* Cyclopentolate 1% + phenylephrine 2.5%.
* Tropicamide 1% + phenylephrine 2.5%.
* Phenylephrine 1% with cyclopentolate 0.2%.

TABLE 4
COMPARISON OF INCREASE IN PUPILLARY DILATION AT 45 AND 60 MINUTES BY MYDRIATIC GROUP

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD Increase in Dilation (mm)</th>
<th></th>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td>45 Minutes</td>
<td>60 Minutes</td>
<td></td>
</tr>
<tr>
<td>Right eye</td>
<td>4.12 ± 0.92</td>
<td>4.50 ± 0.88</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>Left eye</td>
<td>4.20 ± 1.00</td>
<td>4.47 ± 0.90</td>
<td>.092</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye</td>
<td>3.99 ± 0.75</td>
<td>4.09 ± 0.57</td>
<td>.236</td>
<td></td>
</tr>
<tr>
<td>Left eye</td>
<td>4.03 ± 0.73</td>
<td>4.16 ± 0.60</td>
<td>.401</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye</td>
<td>3.67 ± 0.84</td>
<td>4.01 ± 0.94</td>
<td>.017</td>
<td></td>
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<tr>
<td>Left eye</td>
<td>3.72 ± 0.82</td>
<td>3.85 ± 0.94</td>
<td>.379</td>
<td></td>
</tr>
</tbody>
</table>

* Cyclopentolate 1% + phenylephrine 2.5%.
* Tropicamide 1% + phenylephrine 2.5%.
* Phenylephrine 1% with cyclopentolate 0.2%.

right and left eyes were not significantly different within any of the groups (Table 3). There also were no statistically significant differences in pupillary diameter among the three groups.

At 60 minutes, the pupil was dilated even further in most of the eyes. A slightly larger pupillary diameter was achieved in group 1 compared to groups 2 and 3, but this difference was not statistically significant.

Mean increase in pupillary dilation achieved at 45 and 60 minutes is compared in Table 4. Group 1 had maximum pupillary dilation both at 45 and 60 minutes, whereas group 3 had the least pupillary dilation at both endpoints.

Cardiovascular Effects of Mydriatic Regimens

Heart Rate. Mean heart rate at baseline was higher than all of the readings recorded thereafter (Fig. 1). Excluding the baseline records, the range of deviation among the subsequent readings was within 10 beats/minute in all three groups.
Blood Pressure. Mean systolic, diastolic, and blood pressures are shown in Figure 2. The rise in systolic, diastolic, and mean blood pressures was biphasic for groups 1 and 2. The first peak was at 10 to 15 minutes, and the second peak was at 60 minutes.

The relative changes of mean systolic, diastolic, and blood pressures are shown in Figures 3-5. Group 1 demonstrated the highest rise in mean systolic blood pressure with an increase of 10.74%, followed by an increase of 9.17% in group 2. Group 3 recorded the lowest increase of 5.31% (Fig. 3).

Group 1 showed two peaks in mean diastolic blood pressure at 15 minutes (9.94%) and at 60 minutes (13.76%) (Fig. 4). For group 2, there was an initial drop in mean diastolic blood pressure at 5 minutes, followed by a sharp rise at 15 minutes (13.13%), and then a gradual decrease to near baseline.

Mean blood pressure is influenced by both systolic and diastolic blood pressures. An overall higher rise of mean blood pressure was detected in group 1 compared to groups 2 and 3 (Fig. 2). The maximum increase in mean blood pressure occurred at 15 minutes (14.06%, 12.12%, and 10.15% for groups 1, 2, and 3, respectively).

Abdominal Girth and Intolerance to Feeds. There were no significant differences in abdominal girth among the three groups at baseline and in the 24 hours after instillation of the eye drops (Table 5). Eight (20.5%) of the 39 patients in the study demonstrated vomiting or an intolerance to feeds within 24 hours after instillation of eye drops; 4 (50%) of these 8 patients were in group 1, while groups 2 and 3 each had 2 (25%) patients with these symptoms.

DISCUSSION

The use of mydriatic agents during ophthalmic examinations in preterm infants has been associated with hypertension and numerous side effects. In addition, the physical manipulation of the globe during

Figure 1. Mean heart rate response to mydriatic regimens. Squares = group 1 (cyclopentolate 1% + phenylephrine 2.5%), diamonds = group 2 (tropicamide 1% + phenylephrine 2.5%), and triangles = group 3 (phenylephrine 1% with cyclopentolate 0.2%).

Figure 2. Mean systolic, diastolic, and blood pressure response to mydriatic regimens. Squares = group 1 (cyclopentolate 1% + phenylephrine 2.5%), diamonds = group 2 (tropicamide 1% + phenylephrine 2.5%), and triangles = group 3 (phenylephrine 1% with cyclopentolate 0.2%), with the dashed lines at the bottom of the chart representing systolic pressures, the solid lines in the middle of the chart representing mean blood pressures, and the dotted lines at the top of the chart representing mean diastolic pressures.

Figure 3. Relative changes in systolic blood pressure after instillation of mydriatic agents. Black bars = group 1 (cyclopentolate 1% + phenylephrine 2.5%), white bars = group 2 (tropicamide 1% + phenylephrine 2.5%), and gray bars = group 3 (phenylephrine 1% with cyclopentolate 0.2%).
examination has been reported to cause oculocardiac reflex with rebound tachycardia and hypertension.\textsuperscript{10,11} Therefore, it is important to use a mydriatic regimen that dilates well with minimal systemic side effects to enable a quick, thorough examination.

In our study, all three mydriatic regimens achieved a mean pupillary diameter $\geq 6$ mm, which was adequate for examination of the peripheral retina. There was no significant difference in mean pupillary diameter among the three regimens at 45 and 60 minutes. Pupillary dilation was maintained at 60 minutes in both the tropicamide 1\% + phenylephrine 2.5\% (group 2) and the cyclopentolate 0.2\% with phenylephrine 1\% groups (group 3). The cyclopentolate 1\% + phenylephrine 2.5\% (group 1) not only maintained but also had a significant further pupillary dilation at 60 minutes because of the longer cycloplegic effect of cyclopentolate 1\%, which is not required in diagnostic ophthalmic examination. Sindel et al.\textsuperscript{8} reported a net mydriasis of 4.6 $\pm$ 0.8 mm using the phenylephrine 2.5\% + tropicamide 1\% regimen. Our study showed a slightly lower mean mydriasis of 4.09 $\pm$ 0.57 mm in the right eye and 4.16 $\pm$ 0.60 mm in the left eye.

In the cyclopentolate 0.2\% with phenylephrine 1\% regimen (group 3), the mean increase in pupillary dilation was 4.01 $\pm$ 0.9 mm in the right eye and 3.85 $\pm$ 0.94 mm in the left eye, which is a better response compared to Isenberg et al.\textsuperscript{6} who reported a mean mydriasis of 2.8 $\pm$ 0.56 mm. Another study using the same regimen reported a net mydriasis of 2.7 mm.\textsuperscript{7}

Pupillary dilation was greatest in the eyes that received the cyclopentolate 1\% + phenylephrine 2.5\% regimen (group 1). However, this was not statistically significant when compared to the other two regimens.

In all of the study groups, the baseline heart rate was paradoxically the highest. This was probably caused by the method used. The infants were probably sleeping when the local anesthetic drops were applied, followed by the lid speculum, to record the baseline pupillary diameter. Presumably, being awakened abruptly might have caused the rise in heart rate in these infants. This problem was overlooked during the preparation of the protocol. To avoid this technical error, the baseline recordings should be obtained 1 hour prior to the procedure, with infants at rest before measurements are taken. However, excluding the baseline records, the relative rise in mean heart rate after instillation of the mydriatic agent was less than 10 beats/minute, which is comparable to other studies.\textsuperscript{5,8,9}

A double-blind study with 10\% and 2.5\% phenylephrine eye drops found pupillary dilation was adequate with both concentrations; however, a significant rise in blood pressure was noted with the 10\% phenylephrine drops.\textsuperscript{4} Blood pressure remained stable in the infants receiving 2.5\% phenylephrine drops. Another study confirmed the lack of elevated blood pressure with 2.5\% phenylephrine, but pupillary dilation was insufficient.\textsuperscript{4} However, other studies have reported an increase in blood pressure when using 2.5\% phenylephrine combined with tropicamide 0.5\%.\textsuperscript{5,7} In con-
contradict, one study reported no significant increase in blood pressure using the same combination.

We noted a significant increase in blood pressure within 15 minutes after administration of eye drops with the tropicamide 1% + phenylephrine 2.5% regimen (group 2). This finding is in agreement with that of Sindel et al. who recorded a maximum increase of 14.9 ± 9.6%, 15.9 ± 7.8%, and 17.1 ± 10.4% in mean systolic, diastolic, and blood pressures, respectively.

The cyclopentolate 0.2% + phenylephrine 1% regimen (group 3) showed the least effect on blood pressure compared to the other two regimens. Isenberg and Everett also reported a similar finding. In their study, mean blood pressure decreased by 3.8% in the cyclopentolate 0.2% + phenylephrine 1% group while the phenylephrine 2.5% + tropicamide 0.5% group exhibited an increase of 19.6%.

In our study, the cyclopentolate 1% + phenylephrine 2.5% regimen (group 1) had the maximum effect on blood pressure. Some studies using cyclopentolate 0.5% alone reported a reduction in mean blood pressure, while others reported no change in blood pressure with cyclopentolate 1% alone. It appeared that the sympathomimetic effect of phenylephrine was enhanced when a longer-acting parasympatholytic agent was used simultaneously. This may have a potentially dangerous effect on premature infants and distressed newborns in whom there is impaired autoregulation of the cerebral blood flow. It has been suggested that intracranial hemorrhage is related to elevation of systemic blood pressure.

The effect of mydriatic combinations on the gastrointestinal system was compared in this study. Although mean abdominal girth measurements did not show significant changes in any of the mydriatic regimens, 8 (20.5%) of the infants had intolerance to feeds following instillation of the mydriatic eye drops. Four (50%) of these infants were in group 1 (cyclopentolate 1% + phenylephrine 2.5%). The effects of cyclopentolate on gastric secretory function in preterm infants was studied by Isenberg et al. They found cyclopentolate 0.5% significantly decreased gastric acid secretion and volume in infants. The anticholinergic effect of cyclopentolate might adversely affect gastrointestinal motility, leading to vomiting or intolerance to feeds. This adverse effect settled after 12 to 24 hours.

CONCLUSION

Pupillary dilation was adequate in all three mydriatic regimens, with dilation maintained at 60 minutes in all three regimens. Although maximum pupillary dilation was recorded in the cyclopentolate 1% + phenylephrine 2.5% group, this combination caused a significant elevation of systolic, diastolic, and mean blood pressures, which was prolonged, with a significant occurrence of intolerance to feeds. The cyclopentolate 0.2% with phenylephrine 1% combination appears to be the safest mydriatic regimen for preterm infants with dark irides as it provided adequate mydriasis with minimal systemic side effects.

REFERENCES


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**TABLE 5**

**COMPARISON OF ABDOMINAL Girth Before and After Instillation of Mydriatics**

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean ± SD Abdominal Girth (cm)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hours</td>
<td>25.154 ± 1.737</td>
<td>27.238 ± 2.355</td>
<td>26.831 ± 3.024</td>
<td></td>
</tr>
<tr>
<td>12 hours</td>
<td>25.115 ± 1.697</td>
<td>27.123 ± 2.271</td>
<td>27.046 ± 3.167</td>
<td></td>
</tr>
<tr>
<td>18 hours</td>
<td>25.154 ± 1.676</td>
<td>27.085 ± 2.212</td>
<td>26.931 ± 2.990</td>
<td></td>
</tr>
<tr>
<td>24 hours</td>
<td>25.215 ± 1.603</td>
<td>27.123 ± 2.038</td>
<td>27.115 ± 2.888</td>
<td></td>
</tr>
</tbody>
</table>

* Cyclopentolate 1% + phenylephrine 2.5%.
* Tropicamide 1% + phenylephrine 2.5%.
* Phenylephrine 1% with cyclopentolate 0.2%.
REFERENCES