The pressor and mydriatic effects of tropicamide-phenylephrine combination, plain tropicamide, and plain phenylephrine

A randomized, controlled trial

ABSTRACT

Objective
To evaluate the pressor and mydriatic effects of different concentrations of tropicamide and phenylephrine eye drops: tropicamide 0.5% (Mydriacyl), phenylephrine hydrochloride 2.5% (Mydfrin), tropicamide-phenylephrine combination 0.5%/0.5% (Sanmyd-P), and self-prepared mixture (1:1 dilution) of commercially prepared tropicamide 0.5% and phenylephrine 2.5%.

Methods
A prospective, randomized, double-blind study was carried out involving 160 eyes of 80 patients who were randomly assigned into four groups to receive phenylephrine + tropicamide 0.5%/0.5% (Group A), tropicamide + phenylephrine 0.2%/1.25 (Group B), tropicamide 0.5% (Group C), or phenylephrine 2.5% (Group D). The main outcome measures were systolic, diastolic, and mean arterial pressures; pulse rate; and horizontal pupillary diameter determined at 10-, 20-, 30-, 45-, and 60-minute intervals postinstillation. Repeated measures analysis of variance and Tukey’s honestly significant difference were used to analyze outcomes.

Results
There was no significant increase in the systolic and diastolic blood pressure within each group and between groups. The mean increase or decrease in heart rate from baseline did not show a significant difference. Tropicamide-phenylephrine 0.5%/0.5% (Group A) and tropicamide-phenylephrine 0.25%/1.25% (Group B) yielded the highest mean increase in pupil size across time.

Conclusion
Tropicamide-phenylephrine 0.5%/0.5% and tropicamide-phenylephrine 0.25%/1.25% attained better dilation per unit time than the other treatment groups. No significant effect on blood pressure and heart rate was seen in all groups.

Keywords: Tropicamide, Phenylephrine, Mydriatic, Blood pressure, Heart rate
TROPICAMIDE and phenylephrine hydrochloride eye drops are widely used for mydriasis in routine ophthalmoscopic examinations and prior to cataract surgery to achieve maximal pupil dilatation.

Phenylephrine hydrochloride, a sympathomimetic agonist, is a strong alpha-receptor stimulant with little or no beta-receptor effect. Cardiovascular actions of phenylephrine include vasoconstriction of the systemic, pulmonary, and coronary arteries. This leads to reduction in cardiac output and renal, splanchnic, cutaneous, and limb blood flow. Consequently, there is an increase in the systolic and diastolic blood pressure, tachycardia, and reflex bradycardia, side effects that are generally unwanted in the clinic or operating room.

Tropicamide, on the other hand, is a parasympathomimetic antagonist that causes mydriasis and cycloplegia. It is devoid of vasopressor effect, giving it a clear advantage over phenylephrine.

Although either class of drug used alone will produce adequate mydriasis, experience and studies have shown that the use of both a sympathomimetic drug and a parasympathomimetic drug produces maximal mydriasis that is resistant to intense light stimulation. Although topical ophthalmic drops are generally safe to use, they may still reach the systemic circulation and cause unwanted side effects. They are absorbed mainly through the corneal, conjunctival, and the nasal mucosa via the lacrimal system.

Several cases of adverse systemic reactions have been reported following topical application of 10% phenylephrine. Adverse responses include elevated blood pressure, tachycardia, reflex bradycardia, cardiac arrhythmias, and subconjunctival hemorrhage. Kenawy compared phenylephrine 2.5% and 10% in patients undergoing phacoemulsification. The results showed a 10-percent rise in mean systolic blood pressure in both groups 10 to 20 minutes after administration. Similar results were seen in a study by Kumar in patients undergoing vitreoretinal surgery. However, Tang did not find an increase in systemic blood pressure in hypertensive patients dilated with 2.5% phenylephrine and 1% tropicamide.

The alternating instillation of commercially available phenylephrine 2.5% and tropicamide 0.5% given every 5 minutes has become the general practice in the clinic to dilate the pupil. This, however, is time-consuming and inefficient. This study determined if the mixture of commercially prepared phenylephrine and tropicamide is effective and safe. It evaluated the pressor and mydriatic effects of different concentrations of tropicamide and phenylephrine eye drops: tropicamide 0.5% (Mydriacyl, Alcon-Couvreur, Puurs, Belgium), phenylephrine hydrochloride 2.5% (Mydfrin, Alcon Laboratories, Fort Worth, TX, USA), tropicamide-phenylephrine combination 0.5%/0.5% (Sanmyd-P, Santen Pharmaceutical, Osaka, Japan), and self-prepared mixture (1:1 dilution) of commercially prepared tropicamide 0.5% and phenylephrine 2.5%.

**METHODOLOGY**

This is a prospective, double-blind, randomized, controlled trial involving 160 eyes of 80 patients, 20 to 70 years old, scheduled for preoperative cataract evaluation at the outpatient ophthalmology clinic of the University of the Philippines-Philippine General Hospital. Excluded from the study were patients with tearing, history of use of any eye drops within the previous two weeks, contact lens wear, ocular surgery, trauma, and systemic diseases (e.g. diabetes mellitus, hypertension, arthritis, thyroid disease). Patients with afferent pupillary defect (RAPD), irregular pupil, corneal pathology, uveitis, and glaucoma were also excluded.

The following ophthalmologic examinations were done in each case: visual acuity determination, test for RAPD, Schirmer’s test, direct funduscopy, applanation tonometry, and slit-lamp biomicroscopy to determine anterior chamber depth by the Van Herick method. Baseline blood pressure, heart rate, and pupillary diameter were measured prior to instillation of mydriatic eye drops.

Commercially available tropicamide 0.5% drops (Mydriacyl, Alcon-Couvreur, Puurs, Belgium), phenylephrine hydrochloride 2.5% drops (Mydfrin, Alcon Laboratories, Fort Worth, TX, USA) and tropicamide-phenylephrine 0.5%/0.5% drops (Sanmyd-P, Santen Pharmaceutical, Osaka, Japan) were used for the study. The eye drops were transferred by a research assistant into four sterile, identical droptainers using aseptic technique and were labeled as A (tropicamide-phenylephrine 0.5%/0.5%), B (tropicamide-phenylephrine 0.25%/1.25%), C (tropicamide 0.5%), and D (phenylephrine 2.5%). Patients were assigned into four groups using blocked randomization. The mydriatic eye drops were administered in a double-masked manner; neither the patient nor the person administering the eye drops knew which solution was given.

Both eyes of each subject received a drop of proparacaine hydrochloride 2%. Three minutes later, two drops of each mydriatic drug was administered on both eyes at five-minute intervals for a total of 3 doses. The drops were instilled into the inferior cul-de-sac of each eye with the patient looking up. The patient was then asked to close the eyes gently and avoid squeezing the eyelids for 3 minutes. Care was taken to ensure that the dropper tip did not touch the subject’s eye to avoid contamination.

Blood pressure, heart rate, and pupil diameter were measured at 10, 20, 30, 45, and 60 minutes following the final instillation of drops. Blood pressure was measured in the right arm, sitting position, using a standard mercu-
The horizontal pupillary diameter was measured to the nearest 0.5 mm using a standard millimeter ruler and a loupe (Neitz, 4x) for magnification. The technician measuring the blood pressure, pulse rate, and pupil size was blinded as to the mydriatic drops used.

Indirect ophthalmoscopy and applanation tonometry were done after 60 minutes. The subjects were told to report any untoward reactions—headache, palpitations, dyspnea, chest discomfort, sweating, and dryness of mouth—as they occur. The data were subjected to repeated measures analysis of variance. Systolic and diastolic blood pressure, pulse rate, and pupillary dilation were analyzed within each drug group and between drug groups. Post hoc analysis was done using Tukey’s honestly significant difference. A value of $p < .05$ was required for the effects on blood pressure, pulse rate, and pupillary dilation to be considered statistically significant.

**RESULTS**

A total of 180 patients (160 eyes) were enrolled in the study and randomized into four groups of 20 patients each, namely: (A) tropicamide 0.5% + phenylephrine HCl 0.5%, (B) tropicamide 0.25% + phenylephrine HCl 1.25%, (C) tropicamide 0.5% alone, and (D) phenylephrine 2.5% alone.

There was no significant difference in baseline age and sex distribution, vital signs (mean systolic blood pressure, diastolic blood pressure, and heart rate), and predilation pupillary size among the 4 groups (Table 1).

There was no significant increase in systolic blood pressure among the 4 groups from baseline to the 60th minute mark. ANOVA showed a significant decrease in the mean systolic blood pressure from baseline to the 60th minute for all groups ($p = .01$) (Figure 1). Post hoc analysis showed that the systolic blood pressures between the 4 groups varied significantly during the observation period ($p < .05$).

There was a large pressure difference of about 10 mm Hg across the groups. Table 2 shows the post hoc comparison of the significant mean difference in mydriatic effects among the four drugs across time.

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**Table 1. Baseline (predilation) demographic characteristics, blood pressure, and heart rate.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A Tropicamide 0.5% + Phenylephrine 0.5% (n=20)</th>
<th>Group B Tropicamide 0.25% + Phenylephrine 1.25% (n=20)</th>
<th>Group C Tropicamide 0.5% (n=20)</th>
<th>Group D Phenylephrine 2.5% (n=20)</th>
<th>$p^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>24 – 69</td>
<td>21 – 75</td>
<td>20 – 71</td>
<td>29 – 65</td>
<td>.11b</td>
</tr>
<tr>
<td>Mean</td>
<td>46 ± 9</td>
<td>39 ± 12</td>
<td>45 ± 13</td>
<td>47 ± 9</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>.37</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>16</td>
<td>14</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Mean predilation SBP1 (mm Hg)</td>
<td>111 ± 12</td>
<td>109 ± 15</td>
<td>111 ± 13</td>
<td>116 ± 13</td>
<td>.30a</td>
</tr>
<tr>
<td>Mean predilation DBP2 (mm Hg)</td>
<td>72 ± 8</td>
<td>72 ± 10</td>
<td>71 ± 9</td>
<td>76 ± 8</td>
<td>.24a</td>
</tr>
<tr>
<td>Mean predilation HR3</td>
<td>72 ± 11</td>
<td>74 ± 8</td>
<td>70 ± 6</td>
<td>74 ± 6</td>
<td>.24a</td>
</tr>
<tr>
<td>Mean pupil size (OD) (mm)</td>
<td>2.9 ± 0.5</td>
<td>3.1 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td>.34a</td>
</tr>
<tr>
<td>Mean pupil Size (OS) (mm)</td>
<td>2.9 ± 0.5</td>
<td>3.1 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td>.34a</td>
</tr>
</tbody>
</table>

1. systolic blood pressure
2. diastolic blood pressure
3. heart rate

**Table 2. Post hoc comparison of the significant mean difference in mydriatic effects among the four drugs across time.**

<table>
<thead>
<tr>
<th>Drug Comparison</th>
<th>Mean Difference (mm)</th>
<th>$p^a$</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropicamide-phenylephrine 0.5%/0.5% v. tropicamide-phenylephrine 0.25% / 1.25% (A v. B)</td>
<td>−.15</td>
<td>.77</td>
<td>−.56 - .26</td>
</tr>
<tr>
<td>Tropicamide-phenylephrine 0.5%/0.5% v. tropicamide 0.5% (A v. C)</td>
<td>.45</td>
<td>.02a</td>
<td>.04 - .86</td>
</tr>
<tr>
<td>Tropicamide-phenylephrine 0.5%/0.5% v. phenylephrine 2.5% (A v. D)</td>
<td>.87</td>
<td>&lt;.05b</td>
<td>.46 - 1.20</td>
</tr>
<tr>
<td>Tropicamide-phenylephrine 0.25%/1.25% v. tropicamide 0.5% (B v. C)</td>
<td>.60</td>
<td>.001b</td>
<td>.19 - 1.10</td>
</tr>
<tr>
<td>Tropicamide-phenylephrine 0.25%/1.25% v. phenylephrine 2.5% (B v. D)</td>
<td>1.02</td>
<td>&lt;.05b</td>
<td>.61 - 1.40</td>
</tr>
<tr>
<td>Tropicamide 0.5% v. phenylephrine 2.5% (C v. D)</td>
<td>.41</td>
<td>&lt;.05b</td>
<td>.01 - .83</td>
</tr>
</tbody>
</table>

a. significant if $<.05$
b. computed using repeated measures ANOVA

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between Group B and Group D ($p = .035$), with the latter causing a gradual decrease especially noted at 10, 20, and 30 minutes from administration.

No significant difference was seen in the diastolic blood pressures within each group ($p = .43$) and between the 4 groups ($p = .11$), as well as in the mean increase or decrease in heart rate within each group ($p = .78$), and between the 4 groups ($p = .42$) from baseline to 60 minutes postadministration (Figures 2 and 3). None of the patients had tachycardia or bradycardia in the study.

A statistically significant increase in pupillary size (Figure 4) from baseline to 60 minutes postinstillation was seen in all of the 4 groups ($p < .05$). Among the 4 drugs, the mean pupillary size also increased significantly ($p < .05$). Groups A, B, and C all showed quick mydriasis from baseline to the 20th-minute mark then reached plateau thereafter. Group D had a slower onset of pupil dilatation from baseline to 10 minutes, then showed a steady increase up to the 30th-minute mark.

Table 2 shows a post hoc analysis using Tukey’s honestly significant difference for all significant increases in pupil size observed. Among the five significant mean differences in pupil dilatation across time, there was a significant difference in the rate of dilation with group B being faster than group D (mean difference 1.02 mm, 95% CI .61-.1.4, $p < .05$). Groups A and B had the highest mean increase in pupil size across time, although much of the increase was observed within the first 20 minutes of administration, peaking at 10 minutes, and reaching plateau at 30 to 60 minutes.

**DISCUSSION**

A study involving 217 consecutive eyes in the same number of Chinese patients found that tropicamide 1% with phenylephrine 2.5% attained better preoperative mydriasis than tropicamide + phenylephrine 0.5% / 0.5%.
Both did not increase the blood pressure and heart rate. However, this study used only one eye per patient and a different concentration of tropicamide. A local study that compared phenylephrine 2.5% drops with and without the use of cotton pack also did not cause an increase in blood pressure and heart rate. This study involved the use of the same concentration of phenylephrine and was not compared with other mydriatic combinations.

In our study, topical ophthalmic administration of the 4 drugs did not cause a significant increase in mean systolic or diastolic blood pressure and heart rate. One drop of 2.5% solution contains approximately 1.125 mg of phenylephrine. In the average adult, the lowest amount of phenylephrine to produce a pressor effect is 0.4 mg intravenously and 2 mg subcutaneously. The highest safe dosage is 1.5 mg intravenously and 300 mg subcutaneously. Assuming that the entire 1.125 mg is absorbed systemically, it may produce an increase in blood pressure. Although epithelial disruption following topical anesthesia may facilitate absorption of topical eye drops, the amount absorbed systemically depends on the dosage, application route, aqueous or viscous characteristics, dilution by lacrimation, and increased permeability of hyperemic conjunctival epithelium. While certain drugs are rapidly transported from the nasolacrimal system and absorbed into the vascular system, it is possible that a relatively small portion of commercially available phenylephrine is able to do so. This could be because the drug causes local vasoconstriction, there is diminished flow to an area with which it is in contact, or the patient complied well with instructions not to blink.

A drop in systolic blood pressure in all treatment groups was observed. It is possible that this may have occurred as a result of the calming effect of being instructed to sit still with the eyes closed.

Rapidity of dilatation saves time for both patient and physician. This study showed all 4 drug groups increased pupillary size, but it was the tropicamide-phenylephrine 0.5%/0.5% and the self-prepared tropicamide 0.25%-phenylephrine 1.25% groups that produced rapid dilatation and did not have a significant effect on blood pressure. By eliminating the need for multiple instillation of two different drugs, the use of a single eye drop mydriatic combination is convenient in terms of time saved.

In conclusion, both tropicamide-phenylephrine 0.5%/0.5% and tropicamide-phenylephrine 0.25%/1.25% attained better dilation per unit time compared with phenylephrine 2.5% or tropicamide 0.5%. None of the medications caused an increase in the heart rate or blood pressure.

References
5. Kenawy NB, Jabir M. Phenylephrine 2.5% and 10% in phacoemulsification under topical anesthesia: is there an effect on systemic blood pressure? Br J Ophthalmol 2003; 87: 505-506.

Acknowledgment
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