Single Dose of 1% Tropicamide and 10% Phenylephrine for Pupil Dilation

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Objective: *To compare the efficacy of pupil dilation between a single dose and three doses of 1% tropicamide and 10% phenylephrine for binocular indirect ophthalmoscopy.*
Material and Method: *A prospective randomized double-blind clinical controlled trial was conducted. All patients underwent the binocular indirect ophthalmoscopy and met the inclusion criteria were randomized into two groups using block randomization. Group A received a single dose of 1% tropicamide and 10% phenylephrine eye drops, and Group B received three doses of the same drugs. The primary outcome was the horizontal pupil diameter measured by slit-lamp biomicroscope (Haag-Streit model 900) before and at 10, 15, 20, 25 and 30 minutes after eye drop instillation. The clinical equivalence of the efficacy of pupil dilation between the two groups was defined as the difference of less than or equal to 1 mm (-1 mm to +1 mm).*
Results: *Eighty patients (160 eyes) were randomized into 40 patients (80 eyes) in group A and 40 patients (80 eyes) in group B. The mean pupil sizes at baseline of group A were 3.51 $\pm$ 0.63 mm in the right eye and 3.39 $\pm$ 0.67 mm in the left eye. Those in group B were 3.61 $\pm$ 0.67 mm in the right eye and 3.66 $\pm$ 0.72 mm in the left eye. The mean pupil diameters at 30 minutes of group A were 7.34 $\pm$ 0.51mm in the right eye and 7.41 $\pm$ 0.56 mm in the left eye, whereas those of group B were 7.49 $\pm$ 0.45 mm in the right eye and 7.51 $\pm$ 0.40 mm in the left eye. The mean difference of the pupil size between the two groups was 0.15mm (p = 0.175) in the right eye and 0.10mm (p = 0.362) in the left eye. The 95% confidence intervals of the difference in pupil size were -0.36 to 0.07 mm in the right eye and -0.32 to 0.12 mm in the left eye.*
Conclusion: *The 95% confidence interval of the difference in pupil size lay entirely within the range of equivalence. The single dose of 1% tropicamide and 10% phenylephrine was clinically equivalent to the three doses of the same drugs.*

Keywords: *Pupil dilation, Tropicamide, Phenylephrine*

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Pupil dilation is essential for binocular indirect ophthalmoscopy, a routine part of a complete eye examination. The combination of parasympatholytic and sympathomimetic agents has been found to be efficacious in this procedure by synergistic action. Parasympatholytic drug paralyses constrictor pupillae while sympathomimetic drug ensures maximal stimulation of dilator pupillae. Most hospitals use multiple doses of 1% tropicamide and 10% or 2.5% phenylephrine for dilation of the pupil in routine practice, for example, every 5 minutes for 6 times. To the best of our knowledge, there has been no clinical trial on an appropriate regimen for pupil dilation reported. Therefore, the authors were interested in the study to find out the most appropriate dosage for complete ocular examination, based on the finding that pupil diameter of 6 mm or greater was adequate for binocular indirect ophthalmoscopy. The authors hypothesize that a single dose of 1% tropicamide and 10% phenylephrine was adequate for pupil dilation and conducted this prospective randomized clinical controlled trial to compare the efficacy of pupil dilation between the single dose and the three doses of 1%tropicamide and 10%phenylephrine for the binocular indirect ophthalmoscopy and to

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study the time to pupil dilation of 6 mm or greater.

Material and Method

This prospective randomized double-blind clinical controlled trial complied with the International Conference on Harmonization Guideline for Good Clinical Practice and was approved by Khon Kaen University Ethics Committee for Human Research. Patients with complete informed consent discussion and the signed written consent forms were recruited into the present study. Other inclusion criteria included patients aged between 20 and 80 years old, dark iris, and requiring binocular indirect ophthalmoscopy for complete ocular examination. Exclusion criteria included those with a history of ocular trauma, intraocular surgery, or laser treatment, previous eye drop instillation that may affect pupil dilation and ocular diseases that may affect pupil size such as Horner's syndrome, Adies' pupil, glaucoma, and uveitis. Patients with a history of diabetes mellitus, severe hypertension, and cardiovascular diseases were also excluded.

Patients who met the inclusion criteria were randomized into two groups using block randomization. Group A received a single dose of 1% tropicamide followed by a single dose of 10% phenylephrine eye drop 5 minutes later, whereas Group B received three alternate doses of the same drugs every 5 minutes. Punctal occlusion was performed in all patients to decrease systemic absorption and possible cardiovascular side-effects. Patients in group A received artificial tear drop instead of the drugs in the next four drops so that they had the same total six drops as patients in group B. The patients who received the eye drop and the examiner who measured the pupil size were not aware of the eye drop regimen used. Only the research assistant who broke the sealed envelope and instilled the drugs knew the eye drop regimen used and the code was revealed at the end of the present study. The horizontal pupil diameter was measured by slit-lamp biomicroscope (Haag-Streit model 900) with 0.1 mm resolution and reliability test revealed that the instrument had good reproducibility. Pupil size measurement was performed by one of the authors (NC) immediately before 1% tropicamide instillation and at 10, 15, 20, 25 and 30 minutes after that. The mean horizontal pupil diameters measured at 30 minutes in both groups were compared for equivalence. For a one-sided test, equivalence was declared if the lower one-sided confidence limit exceeded the defined level[1]. The authors chose to use the one-sided test in the present study because the authors wanted to confirm that a single dose is not inferior to the three-dose regimen. Equivalence or superiority are both regarded as positive outcomes. In addition, the time to pupil dilation equal to or greater than 6 mm at 10, 15, 20, 25, and 30 minutes after the first eye drop instillation was also recorded in number and percentage of eyes.

Statistical analysis

Demographic data such as age and gender were reported in percentage and compared between the two groups using Pearson Chi-Square test, whereas the mean age and horizontal pupil sizes were compared using independent t-test. To investigate the efficacy of the different regimen, the mean horizontal pupil diameters measured at 30 minutes was compared using independent t-test. Statistical significance was taken as $p < 0.05$. The clinical equivalence of the efficacy of pupil dilation between the two groups was defined as the difference of equal to or less than 1 mm (-1 mm to +1 mm). A p-value of less than 0.05 was considered significant differences.

Results

Eighty patients (160 eyes) were recruited in the present study. There were 35 males (43.75%) and 45 females (56.25%). All patients were Thai and ages ranged from 24 to 78 years with the mean age of 53.36 $\pm$ 14.05 years. Patients were randomized into two groups, group A and group B, 40 patients (80 eyes) in each group. The patients in group A received a single dose of 1% tropicamide and 10% phenylephrine, whereas those in group B received three alternate doses of the same drugs.

Demographic data of the patients in both groups are demonstrated in Table 1. The mean age of the patients was 54.65 $\pm$ 13.98 years in group A and 52.74 $\pm$ 14.34 years in group B. The difference was not statistically significant using the independent sample t-test. There were 21 males (52.5%) and 19 females (47.5%) in group A, whereas these were 14 males (35%) and 26 females (65%) in group B. The difference was not statistically significant using Pearson Chi-Square test.

The baseline pupil sizes in group A were 3.51 $\pm$ 0.63 mm in the right eye and 3.39 $\pm$ 0.67 mm in the left eye. Those in group B were 3.61 $\pm$ 0.67 mm in the right eye and 3.66 $\pm$ 0.72 mm in the left eye. There was no statistically significant difference between the two groups using unpaired t-test. At 30 minutes the mean pupil diameters of group A were 7.34 $\pm$ 0.51 mm in the right eye and 7.41 $\pm$ 0.56 mm in the left eye, whereas

Table 1. Demographic data of the patients in both groups

Demographic data		Group A (n = 40)	Group B (n = 40)	p-value
Age (years)		54.38 ± 14.08	52.83 ± 14.37	0.627
Sex	Male	21 (52.5%)	14 (35%)	0.115
	Female	19 (47.5%)	26 (65%)	
Baseline pupil size (mm)				
	Right eye	3.51 ± 0.63	3.61 ± 0.67	0.562
	Left eye	3.39 ± 0.67	3.66 ± 0.72	0.091

Values are the mean ± SD
Statistical significant difference at p value < 0.05

Table 2. The mean pupil size at 30 minutes after instillation in both groups

Pupil size (mm)	Group A (n = 40)	Group B (n = 40)	p-value	Mean difference	95%CI* Lower	Upper
Right eye	7.34 ± 0.51	7.49 ± 0.45	0.175	0.15	-0.36	0.07
Left eye	7.41 ± 0.56	7.51 ± 0.40	0.362	0.10	-0.32	0.12

* The 95% confidence interval of the difference
Values are the mean ± SD
Statistical significant difference at p-value < 0.05

Table 3. The number and percentage of right eyes in both groups that had pupil size of 6 mm or greater at different time

Time after first eye drop instillation (minutes)	Group A (n = 40) No. (Percent)	Group B (n = 40) No. (Percent)
10	8 (20%)	18 (45%)
15	29 (72.5%)	34 (85%)
20	38 (95%)	40 (100%)
25	40 (100%)	40 (100%)
30	40 (100%)	40 (100%)

Table 4. The number and percentage of left eyes in both groups that had pupil size of 6 mm or greater at different time

Time after first eye drop instillation (minutes)	Group A (n = 40) No. (Percent)	Group B (n = 40) No. (Percent)
10	8 (20%)	16 (40%)
15	29 (72.5%)	35 (87.5%)
20	35 (87.5%)	40 (100%)
25	38 (95%)	40 (100%)
30	39 (97.5%)	40 (100%)

those in group B were 7.49 ± 0.45 mm in the right eye and 7.51 ± 0.40 mm in the left eye. The mean differences of the pupil size between the two groups were 0.15 mm in the right eye and 0.10 mm in the left eye. The 95% confidence intervals of the difference in pupil size were -0.36 to 0.07 mm in the right eye and -0.32 to 0.12 mm in the left eye (Table 2).

At 15 minutes after the first instillation, 72.5% of both right and left eyes from participants in group A had pupil dilation of 6 mm or greater, whereas 85% of the right eye and 87.5% of the left eye in group B did. There was no statistically significant difference between the two groups. Although there was one (2.5%) out of 40 left eyes in group A who had pupil dilation less than 6 mm at 30 minutes, there was also no statistically significant difference between the two groups (Table 3 and 4).

Discussion

Tropicamide has its peak action at 25-30 minutes after instillation, whereas phenylephrine has its peak effect at 15-60 minutes[2]. This indicates that time to maximum dilation is approximately 25-30 minutes after a single dose instillation of combination of these two drugs. Sinclair et al[3] advocated the use of tropicamide and phenylephrine as the most appropriate drugs used for pupil dilation. They reported 98.8% of patients had adequate pupil dilation with 0.8% tropicamide and 5% phenylephrine and found that a single dose of the appropriate drugs could dilate pupil large enough for indirect ophthalmoscopy. Literature review also supported that a single dose of 2.5% phenylephrine and 0.5-1%tropicamide resulted in pupil dilation adequate for ocular examination[4].

Kergoat et al[5] compared the efficacy of a single dose of the combined 5% phenylephrine -0.8% tropicamide eye drop (Phenyltrope) and 1% tropicamide eye drop for pupil dilation in healthy volunteers aged 20-36 years and found that the combined drug had a faster onset of action. However, there was no significant difference in efficacy between both groups.

Apt and Henrick[6] studied the benefit of 0.5% proparacaine eye drop prior to the mydriatic drugs in 80 patients divided into three groups. Each group received a single dose of 0.5% cyclopentolate with 2.5% phenylephrine, 0.5% tropicamide with 2.5% phenylephrine and 1%tropicamide with 2.5% phenylephrine. They reported that pupil size of 7 mm had been reached within 1 hour in all three groups after one drop of 0.5% proparacaine and single dose of the mydriatic drugs. They concluded that a single dose regimen was economical and reduced the chance of drug toxicity.

Yospaiboon et al[7] compared the efficacy of 10% and 2.5% epinephrine in 564 darkly pigmented irides patients. Patients were randomized into two groups. Patients in group 1 received a single dose of 1% tropicamide and 10% phenylephrine whereas those in group 2 received a single dose of 1% tropicamide and 2.5% phenylephrine. One hour after the instillation, the mean pupil diameter in group 1 was greater than group 2 with statistically significant difference ($p < 0.05$). However, it is also noted that after a single dose instillation, the mean pupil diameters in both groups were greater than 6 mm, which was considered as adequate for indirect ophthalmoscopy.

Although there have been many reports on adequacy of a single dose regimen for indirect ophthalmoscopy[3-6], to the best of our knowledge, there has been no study on an equivalent trial comparing the efficacy of the single dose with the multiple dose regimen. The present study compared the efficacy of pupil dilation between a single dose and three-dose regimen of 1% tropicamide and 10% phenylephrine. The end point was the horizontal pupil diameter measured at 30 minutes after the first eye drop instillation. The result demonstrated that the 95% confidence intervals of the difference in pupil size between the two groups were - 0.36 to 0.07 mm in the right eye and -0.32 to 0.12 mm in the left eye. This lay entirely within the range of equivalence (-1 mm to +1 mm) and was concluded that a single dose was not inferior to the three-dose regimen. The result was in accordance with the previous reports on adequacy of a single dose regimen for pupil dilation[3-6].

In terms of systemic side effects, the British National Formulary[8] recommends caution in the use of 10% phenylephrine, particularly in elderly patients and those with hypertension. Reported systemic side-effects of 10% phenylephrine include a rise in systolic and diastolic blood pressure, tachycardia, reflex bradycardia, ventricular arrhythmia, occipital headache, and subarachnoid hemorrhage[9-17]. The use of a single dose regimen reduced the chance of systemic side effect. This was evidenced by the authors' previous study[7] that reported no statistically significant increase in mean blood pressure and pulse rate of the patients receiving a single dose of 10% phenylephrine. This finding was also reported by Chin[18], Symons[19], and Malhotra[20].

In terms of the time to pupil dilation of 6 mm or greater, which was considered as appropriate for

fundus examination, it was found that most of the patients in both groups had reached a 6 mm pupil size 15 minutes after the first eye drop instillation. Furthermore, all patients except one in group A had pupil dilation greater than 6 mm at 30 minutes after the first eye drop instillation.

In conclusion, the 95% confidence interval of the difference in pupil size lay entirely within the range of equivalence. The single dose of 1% tropicamide and 10% phenylephrine was clinically equivalent to the three-dose regimen of the same drugs. Therefore, the use of a single dose of 1% tropicamide and 10% phenylephrine is effective for pupil dilation. Moreover, it is economical and time saving due to eliminating the need for multiple dose instillations, and safe because it reduces the chance of systemic side effects.

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การขยายรูม่านตาด้วยการหยอดยา 1% tropicamide ร่วมกับ 10% phenylephrine ครั้งเดียว

ธนภัทร รัตนภากร, ยศอนันต์ ยศไพบูลย์, ณัฏฐิรา ชัยศรีสวัสดิ์สุข

วัตถุประสงค์: *เพื่อเปรียบเทียบถึงประสิทธิภาพในการขยายม่านตาด้วยยาหยอดตา 1% tropicamide ร่วมกับ 10% phenylephrine ระหว่างการหยอดยาครั้งเดียวและสามครั้ง ในการตรวจจอตาด้วย binocular indirect ophthalmoscopy*

วัสดุและวิธีการ: *เป็นการศึกษาแบบ randomized double-blinded โดยผู้ป่วยที่ต้องได้รับการตรวจ binocular indirect ophthalmoscopy และเข้าเกณฑ์การศึกษา จะได้รับการแบ่งออกเป็นสองกลุ่ม ด้วยการสุ่ม ได้แก่ กลุ่ม A ได้รับการหยอดยา 1% tropicamide ร่วมกับ 10% phenylephrine ครั้งเดียว และกลุ่ม B ได้รับการหยอดยาทั้งสองดังกล่าวจำนวนสามครั้ง ผลที่ต้องการวัด คือ ขนาดรูม่านตาในแนวนอนจากการวัดด้วย slit-lamp biomicroscope ก่อนการให้ยา และที่ 10, 15, 20, 25, 30 นาทีหลังได้รับยา ประสิทธิภาพของการขยายรูม่านตาในระหว่างสองกลุ่มถือว่าไม่แตกต่างกัน ถ้าความแตกต่างของขนาดรูม่านตาระหว่าง 2 กลุ่มน้อยกว่าหรือเท่ากับ 1 มิลลิเมตร (-1 ถึง +1 มิลลิเมตร)*

ผลการศึกษา: *ผู้ป่วยที่เข้ารับการศึกษามีจำนวน 80 คน (160 ตา) แบ่งเป็นสองกลุ่ม ๆ ละ 40 คน (80 ตา) ค่าเฉลี่ยของขนาดรูม่านตาข้างขวาและข้างซ้าย ก่อนการหยอดยาในกลุ่ม A เท่ากับ 3.51 $\pm$ 0.63 มิลลิเมตร และ 3.39 $\pm$ 0.67 มิลลิเมตร ตามลำดับ ค่าเฉลี่ยของขนาดรูม่านตาข้างขวาและข้างซ้าย ก่อนการหยอดยาในกลุ่ม B เท่ากับ 3.61 $\pm$ 0.67 มิลลิเมตร และ 3.66 $\pm$ 0.72 มิลลิเมตร ตามลำดับ ค่าเฉลี่ยของขนาดรูม่านตาข้างขวาและข้างซ้ายที่ 30 นาทีหลังหยอดยา ในกลุ่ม A เท่ากับ 7.34 $\pm$ 0.51 มิลลิเมตร และ 7.41 $\pm$ 0.56 มิลลิเมตร ตามลำดับ ค่าเฉลี่ยของขนาดรูม่านตาข้างขวาและข้างซ้ายที่ 30 นาทีหลังหยอดยา ในกลุ่ม B เท่ากับ 7.49 $\pm$ 0.45 มิลลิเมตร และ 7.51 $\pm$ 0.40 มิลลิเมตร ตามลำดับ ค่าเฉลี่ยของความแตกต่างของขนาดรูม่านตาในทั้งสองกลุ่มในตาขวาเท่ากับ 0.15 มิลลิเมตร (p = 0.175) ในตาซ้ายเท่ากับ 0.10 มิลลิเมตร (p = 0.362) ค่าความเชื่อมั่นที่ร้อยละ 95 ของความแตกต่างของขนาดรูม่านตาของตาขวาและตาซ้ายอยู่ระหว่าง -0.36 ถึง 0.07 มิลลิเมตร และ -0.32 ถึง 0.12 มิลลิเมตร ตามลำดับ*

สรุป: *ค่าความเชื่อมั่นที่ร้อยละ 95 ของความแตกต่างของขนาดรูม่านตาอยู่ในช่วงของ equivalence ดังนั้นประสิทธิภาพในการขยายม่านตาด้วยยาหยอดตา 1% tropicamide ร่วมกับ 10% phenylephrine ในการหยอดยาครั้งเดียวเทียบเท่ากับการหยอดยาสามครั้ง*