# Randomized Double-blind Study of Phenylephrine 2.5% vs 10% on Pupillary Dilation

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***Purpose :*** *To compare the efficacy of phenylephrine 2.5% versus 10% on pupillary dilation, and also compare their side-effects.*
***Method :*** *Patients at the Eye Clinic Srinagarind Hospital were randomized into two groups. Patients in group 1 received 1% tropicamide and 10% phenylephrine, whereas those in group 2 received 1% tropicamide and 2.5% phenylephrine. Pupil diameter, blood pressure and heart rate were measured before and after eyedrop instillation.*
***Results :*** *Five hundred and sixty four patients were randomized into 293 patients (group 1) and 271 patients (group 2), using simple random sampling method. Mean pupil diameters before instillation in group 1 were 4.43 $\pm$ 1.13 mm in the right eye and 4.31 $\pm$ 0.95 mm in the left eye, whereas those in group 2 were 4.45 $\pm$ 1.0 mm in the right eye and 4.32 $\pm$ 0.92 mm in the left eye. After the instillation, the mean pupil diameters in group 1 were 7.58 $\pm$ 0.96 mm in the right eye and 7.60 $\pm$ 1.03 mm in the left eye, whereas those in group 2 were 7.17 $\pm$ 1.04 mm in the right eye and 7.07 $\pm$ 1.06 mm in the left eye. The difference was statistically significant ($P < 0.05$). There was no significant difference in mean systolic and diastolic blood pressure after instillation between the two groups. However, the mean heart rate after instillation in group 1 was greater than the value in group 2 with statistically significant difference.*
***Conclusion :*** *Pupillary dilation with 1% tropicamide and 10% phenylephrine is more effective than 1% tropicamide and 2.5% phenylephrine with statistically significant difference. After single dose instillation, there was no significant difference in the mean blood pressure between the two groups.*

***Keywords :*** *Phenylephrine, Pupillary dilation, Side effect*

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Dilation of the pupil is considered a routine part of a complete eye examination. The combination of 1% tropicamide and 10% phenylephrine has been found to be efficacious in this procedure. Phenylephrine ensures maximal stimulation of dilator pupillae while tropicamide paralyses constrictor pupillae. Both of them work in synergistic action. However, the British National Formulary[1] 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 arrythmia, occipital headache, and subarachnoid hemorrhage[2-10]. In prospective randomised trials in Caucasians, 2.5% phenylephrine has been found to be as effective as 10% phenylephrine, with fewer systemic side-effects[11-13]. On the other hand, there have been various reports indicating that in dark irides, 10% phenylephrine was more effective than 2.5% phenylephrine in maintaining mydriasis during cataract surgery[14]. Since there has been no report with a large enough sample size to demonstrate the superiority of 10% phenylephrine, the authors conducted a randomized double-blind clinical trial in a large population with dark irides to assess whether 10% phenylephrine was more effective than 2.5% phenylephrine in pupil-

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lary dilation for a complete eye examination.

**Patients and Method**

The present study complied with the International Conference on Harmonization Guideline for Good Clinical Practice and was approved by Khon Kaen University Ethics Committee. Patients with complete informed consent discussion and signed written informed consent forms were recruited into the study. Exclusion criteria included those with a history of intraocular surgery or laser treatment, previous eyedrops instillation that may affect pupillary dilation, and ocular diseases that may affect pupil size such as glaucoma and iritis. Those patients with a history of diabetes mellitus, severe hypertension and cardiovascular diseases were also excluded.

All patients first received one drop of 1% tropicamide and 30 minutes later one drop of 10% or 2.5% phenylephrine by simple random allocation. The pupil sizes were measured using an auto-keratorefractor (Cannon RK2 ) with 0.1 mm resolution. A reliability test revealed that the instrument had good reproducibility.

The examiner who measured the pupil size was not aware of the eyedrop regime used. The patients who received the eye drop and the research assistant who instilled the eyedrop were also not aware of the regime. The 10% and 2.5% phenylephrine eyedrops were prepared in identical bottles and labelled in code A and B by a pharmacist. Only the pharmacist knew the eyedrop regime used and the code was revealed at the end of the study.

Pupil measurement was performed immediately before 1% tropicamide, 30 minutes after 1% tropicamide (before 10% or 2.5% phenylephrine) and 30 minutes after 10% or 2.5% phenylephrine. Using a vital sign monitor (Visomat compact ), systolic and diastolic blood pressure and heart rate were also measured before and 30 minutes after 10% phenylephrine or 2.5% phenylephrine.

***Statistical analysis***

To investigate the efficacy of both phenylephrine eyedrops, the mean pupil size was compared between the two groups using the independent t-test. In addition, changes in blood pressure and heart rate were also investigated by comparing the mean change in systolic and diastolic blood pressure and heart rate before and after both phenylephrine eyedrops with unpaired t-test. Statistical significance was taken as $P < 0.05$.

**Results**

Five hundred and sixty four patients were included in the study, 56.9%(316 patients) of whom were female. The mean age was 51.1±16.79 years (range 5-87 years). Two hundred and ninety three patients received 10% phenylephrine and 271 patients received 2.5% phenylephrine. The patients' demographic data is shown in Table 1. There was no statistically significant difference in these data between the two groups using unpaired t-test.

The mean pupil size at baseline measurement for 10% phenylephrine group was 4.43 ± 1.13 mm in the right eyes and 4.31 ± 0.95 mm in the left eyes, whereas those in the 2.5% phenylephrine group was 4.45 ± 1.0 mm in the right eyes and 4.32 ± 0.92 mm in the left eyes. There was no statistically significant difference between the two groups using unpaired t-test.

After 1% tropicamide the mean pupil size of the 10% phenylephrine group was 6.46 + 0.99 mm in the right eyes and 6.45 + 0.99 mm in the left eyes, whereas those in the 2.5% phenylephrine group was 6.38 + 0.96 mm in the right eyes and 6.34 + 1.01 mm in the left eyes (Table 2). There was also no statistically significant difference between the two groups.

The mean difference of the pupil size between before and after phenylephrine for the 10% phenylephrine group was greater than those for the 2.5% phenylephrine with a statistically significant difference using unpaired t-test (Table 3).

In the present study there was no difference between the two groups in the mean systolic or diastolic blood pressure both before and after phenylephrine. However, the mean heart rate after phenylephrine for the 10% phenylephrine group was greater than that

**Table 1.** Demographic data of the patients in both groups

| Demographic data | 10% Phenylephrine Group (n=293) | 25% Phenylephrine Group (n=271) | P-value |
|---|---|---|---|
| Age (years) | 49.93±17.03 | 52.37±16.46 | NS |
| Sex Male | 124 (42.3%) | 125 (46.1%) | |
| Female | 169 (57.7%) | 146 (53.9%) | |
| Baseline pupil size (mm) | | | |
| Right eye | 4.43±1.13 | 4.45±1.0 | NS |
| Left eye | 4.31±0.95 | 4.32±0.92 | NS |
| Blood pressure (mmHg) | | | |
| Systolic | 121.66±21.76 | 123.17±21.73 | NS |
| Diastolic | 77.68±13.26 | 77.17±12.86 | NS |
| Heart rate (bpm) | 77.99±15.36 | 76.51±13.04 | NS |

Values are the mean ± SD
NS, no significant difference (P > 0.05)

**Table 2.** Pupil size after tropicamide and phenylephrine in both groups

| Pupil size (mm) | 10% Phenylephrine Group (n=293) | 25% Phenylephrine Group (n=271) |
|---|---|---|
| Right eyes | | |
| baseline | 4.43±1.13 | 4.45±1.0 |
| after T | 6.46±0.99 | 6.38±0.96 |
| after P | 7.58±0.96 | 7.17±1.04 |
| Left eyes | | |
| baseline | 4.31±0.95 | 4.32±0.92 |
| after T | 6.45±0.99 | 6.34±1.01 |
| after P | 7.60±1.03 | 7.07±1.06 |

Values are the mean ± SD
T = tropicamide, P = phenylephrine

**Table 3.** Change in pupil size after tropicamide and phenylephrine in both groups

| Pupil size (mm) | 10% Phenylephrine Group (n=293) | 2.5% Phenylephrine Group (n=271) | P-value |
|---|---|---|---|
| Right eyes | | | |
| ΔT | 2.03±0.95 | 1.93±0.94 | 0.183 |
| ΔP | 1.12±0.68 | 0.79±0.59 | <0.001 |
| Left eyes | | | |
| ΔT | 2.14±0.91 | 2.02±0.94 | 0.135 |
| ΔP | 1.16±0.79 | 0.73±0.57 | <0.001 |

Values are the mean ± SD
ΔT = difference of pupil size between before and after tropicamide
ΔP = difference of pupil size between before and after phenylephrine
Significant difference at $P < 0.05$

**Table 4.** Blood pressure and heart rate after phenylephrine in both groups

| | 10% Phenylephirine Group (n=293) | 2.5% Phenylephrine Group (n=271) | P-value |
|---|---|---|---|
| Systolic BP (mmHg) | | | |
| before P | 121.66±21.76 | 123.17±21.23 | NS |
| after P | 122.29±22.02 | 124.48±21.14 | 0.206 |
| Diastolic BP (mmHg) | | | |
| before P | 77.68±13.26 | 77.17±12.86 | NS |
| after P | 79.20±13.68 | 78.17±12.09 | 0.337 |
| Heart rate (bpm) | | | |
| before P | 77.99±15.36 | 76.51±13.04 | NS |
| after P | 80.84±15.99 | 77.72±12.96 | 0.005 |

Values are the mean ± SD
BP = blood pressure P=phenylephrine
NS, no significant difference (P>0.05)

for the 2.5% phenylephrine group with a statistically significant difference (Table 4).

## Discussion

In a prospective randomized double-blind clinical trial there was a large enough sample size to demonstrate that in darkly pigmented irides 10% phenylephrine appears to be more effective than 2.5% phenylephrine in pupillary dilation. This does not agree with previous reports that studied in lightly pigmented irides. Neuhaus and Hepler[11] studied in a group of 11 patients and found that 10% phenylephrine did not produce significantly more mydriasis than 2.5% phenylephrine in the general population. In a prospective randomized trial, Tanner and Casswell[12] compared the efficacy of 10% phenylephrine (53 patients) versus 2.5% phenylephrine (62 patients) and demonstrated that 2.5% phenylephrine was as effective as 10% phenylephrine in the initiation and maintenance of mydriasis during cataract surgery. Weiss et al[13] also conducted a prospective double-blind study to compare the clinical efficacy of 2.5% phenylephrine and 10% phenylephrine for pupillary dilation in patients with diabetes. They found no statistically significant difference in the amount of pupillary dilation between the two groups. On the other hand, Duffin et al[14] revealed that in darkly pigment irides 10% viscous solution of phenylephrine hydrochloride was more effective than 2.5% aqueous solution of phenylephrine hydrochloride in maintaining mydriasis during extracapsular cataract surgery.

This seems to be that iris pigment is a significant variable in pupillary mydriasis. Howard and Lee[15] first reported the difference between Caucasians with light colored irides and Chinese with dark irides. They demonstrated that lightly pigmented irides responded to smaller doses of mydriatic drugs and yielded a larger mydriasis, which developed more rapidly. Chen and Poth[16] also observed that ephedrine was considerably less active in dilating the pupils in Americans of African and Chinese descent than in white Americans. Angenent and Koelle[17] postulated that the difference might be due to increased destruction of the sympathetic transmitter in pigmented irides. From an experimental study in rabbits they found that adrenaline was oxidized more rapidly by homogenates of pigmented irides than of albino irides. This was attributed to the presence of a more active catechol-oxidase system. Emiru[18] postulated that phenylephrine had to be absorbed through the cornea into the aqueous humor and then absorbed by the iris surface. In darkly pigmented irides the anterior layer of the iris was thicker

due to denser iris chromatophores and had fewer crypts. This made phenylephrine absorption much slower than in lightly pigmented irides which had a thinner anterior layer and more numerous and larger crypts.

In the present study the authors have shown no statistically significant difference in the rise in blood pressure produced by both 10% and 2.5% phenylephrine. This agrees with all the previous reports. Chin et al[18] showed that 2.5% and 10% topical aqueous phenylephrine produced a significant rise in blood pressure in previously non-hypertensive patients and no significant change in blood pressure in known hypertensive patients. However, no significant difference between the two groups (2.5% vs 10%) was shown. Symons et al[19] also reported no significant change in the mean systolic and diastolic blood pressure in patients receiving 10% phenylephrine. In addition, Malhotra et al[20] demonstrated no significant difference in the rise in blood pressure between the two groups. In the present study, there was no statistically significant difference in the mean systolic and diastolic blood pressure after phenylephrine between the two groups. This may be attributed to the single dose regime that makes the concentration of phenylephrine too low for any significant systemic effect.

In conclusion, the authors have demonstrated that in darkly pigmented irides patients with no history of diabetes mellitus, severe hypertension and cardiovascular diseases, 10% phenylephrine appeared to be more effective than 2.5% phenylephrine in pupillary dilation. Furthermore, using a single dose regime, there was no significant difference in the rise in blood pressure between the two groups.

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***การศึกษาเปรียบเทียบการใช้ 2.5% และ10% phenylephrine ในการขยายรูม่านตา***

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***วัตถุประสงค์*** *: เพื่อศึกษาเปรียบเทียบผลการขยายรูม่านตาของ 2.5% และ 10% phenylephrine และศึกษาเปรียบเทียบผลข้างเคียงของการใช้ยาดังกล่าว*

***วิธีวิจัย*** *: ศึกษาในผู้ป่วยที่มารับการตรวจตาที่แผนกผู้ป่วยนอก โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น ผู้ป่วยได้รับการสุ่มเป็น 2 กลุ่ม กลุ่มที่ 1 ได้รับการหยอดยา 1% tropicamide และ 10% phenylephrine กลุ่มที่ 2 ได้ยา 1% tropicamide และ 2.5% phenylephrine ทำการวัดขนาดรูม่านตาก่อนและหลังหยอดยา วัดความดันโลหิต และอัตราการเต้นของหัวใจทั้งก่อนและหลังหยอดยา*

***ผลการวิจัย*** *: ผู้ป่วย 564 ราย ได้รับการสุ่มแบบ simple random sampling เป็นผู้ป่วยกลุ่มที่ 1: 293 ราย และกลุ่มที่ 2: 271 ราย ขนาดรูม่านตาเฉลี่ยของผู้ป่วยก่อนได้รับการหยอดยาในกลุ่มที่ 1 ตาขวาเท่ากับ 4.43±1.13 มม. และตาซ้ายเท่ากับ 4.31±0.95 มม. ส่วนในกลุ่มที่ 2 ตาขวาเท่ากับ 4.45±1.0 มม. และตาซ้ายเท่ากับ 4.32±0.92 มม. หลังได้รับการหยอดยาขนาดรูม่านตาเฉลี่ยของผู้ป่วยกลุ่มที่ 1 ตาขวาเท่ากับ 7.58±0.96 มม. และตาซ้ายเท่ากับ 7.60±1.03 มม. ส่วนในกลุ่มที่ 2 ตาขวาเท่ากับ 7.17±1.04 มม. และตาซ้ายเท่ากับ 7.07±1.06 มม. พบว่าค่าเฉลี่ยของขนาดรูม่านตาในกลุ่มที่ 1 มากกว่าค่าเฉลี่ยในกลุ่มที่ 2 อย่างมีนัยสำคัญทางสถิติ ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างค่าเฉลี่ยความดันโลหิต systolic และ diastolic ของทั้ง 2 กลุ่ม แต่พบว่าค่าเฉลี่ยอัตราการเต้นของหัวใจในกลุ่มที่ 1 มีค่ามากกว่าค่าเฉลี่ยในกลุ่มที่ 2 อย่างมีนัยสำคัญทางสถิติ*

***สรุป*** *: การหยอดยาขยายรูม่านตาด้วย 1% tropicamide ร่วมกับ 10% phenylephrine มีประสิทธิภาพมากกว่า การใช้ 1% tropicamide ร่วมกับ 2.5% phenylephrine อย่างมีนัยสำคัญทางสถิติ ค่าเฉลี่ยความดันโลหิตหลังหยอดยาไม่แตกต่างกัน*