2.5% and 10% Phenylephrine for Mydriasis in Diabetic Patients with Darkly Pigmented Irides

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Objective: *To compare the clinical efficacy and systemic side effects of 2.5% and 10% phenylephrine for mydriasis in diabetic patient with darkly pigmented irides.*

Material and Method: *A prospective randomized double-blind controlled trial was conducted. One hundred diabetic patients were randomly allocated into 2.5% and 10% phenylephrine groups by block randomization. Pupil diameter, blood pressure and heart rate were measured before and after eye drop instillations.*

Results: *The mean pupil diameters after instillation in the right eye were 7.05 $\pm$ 0.71 mm (2.5% phenylephrine group) and 7.40 $\pm$ 0.72 mm (10% phenylephrine group, p = 0.02) and in the left eye were 7.05 $\pm$ 0.72 mm (2.5% phenylephrine group) and 7.39 $\pm$ 0.72 mm (10% phenylephrine group, p = 0.02). There was no clinically significant difference in mean heart rate, mean systolic and diastolic blood pressure.*

Conclusion*: In diabetic patients with darkly pigmented irides, 10% phenylephrine is more effective than 2.5% phenylephrine with statistical significance. The authors recommend a single dose of 10% phenyleprine for mydriasis in these patients. However, the lower concentration is recommended for use in those who exhibit a higher prevalence of significant vascular disease and autonomic dysfunction and seem to be susceptible to severe adverse reaction of phenylephrine.*

Keywords: *Phenylephrine, Mydriasis, Diabetes*

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Dilation of the pupil is an essential part of diabetic retinopathy screening for early diagnosis and blindness prevention. 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. 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[2-4]. In prospective randomised trials in healthy subjects with lightly pigmented irides, 2.5% phenylephrine has been found to be as effective as 10% phenylephrine, and recommended for routine use because of less systemic side effects[5,6]. On the other hand, there have been various reports indicating that in dark irides, 10% phenylephrine was more effective than 2.5% phenylephrine in mydriasis[7,8]. In diabetic patients with lightly pigmented irides, 2.5% phenylephrine has also been found to be as effective as 10% phenylephrine in production of mydriasis with fewer systemic side-effects[9,10]. Since there has been no comparative study in diabetic patients with darkly pigmented irides, the authors conducted a prospectively randomized double-blind controlled trial to evaluate the clinical efficacy and systemic side effects of 2.5% and 10% phenylephrine for mydriasis in diabetic patients with darkly pigmented irides.

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Material and Method

This present study was conducted according to the principles expressed in the Declaration of Helsinki. It was reviewed and approved by the Khon Kaen University ethics committee for human

research. The sample size was calculated from the formula $2s^2(Z_{(1-\alpha)} + Z_{(1-\beta/2)})^2/\Delta^2$. The authors used the standard deviation of 1.06 from the previous study[8]. At 95% confidence level, a power of 90%, and an acceptable pupil size difference of 1 mm, the required number of patients per treatment group was 24. Since there were many patients eligible for the study and the procedures did no harm to the patients, the authors decided to increase the amount of recruited patients to be 50 per group in order to increase the precision.

One hundred and forty six diabetic patients were recruited from May to July 2007. Forty six patients were excluded due to a history of intraocular surgery or laser treatment, any ocular diseases that might affect pupil size such as glaucoma, uveitis, Horner's syndrome, Adies' pupil, iris neovascularization, history of allergy to any drug used, and hypertension. One hundred patients with complete informed consent were randomly allocated into 2.5% and 10% phenylephrine groups by block randomization. The trial profile is summarized in Fig. 1. The random allocation sequence was generated using computer-generated random numbers with randomly varying blocks (SAS software, SAS Institute, Inc., Cary, NC). The random allocation was concealed by using sealed opaque envelopes numbering sequentially using the sequence described above, and kept by a research assistant. A pharmacist prepared 2.5% and 10% phenylephrine and labeled code A and B respectively. He was the only one who knew which code is 2.5% or 10% phenylephrine. The researchers and patients did not know the code and unblinding was done at the end of the present study.

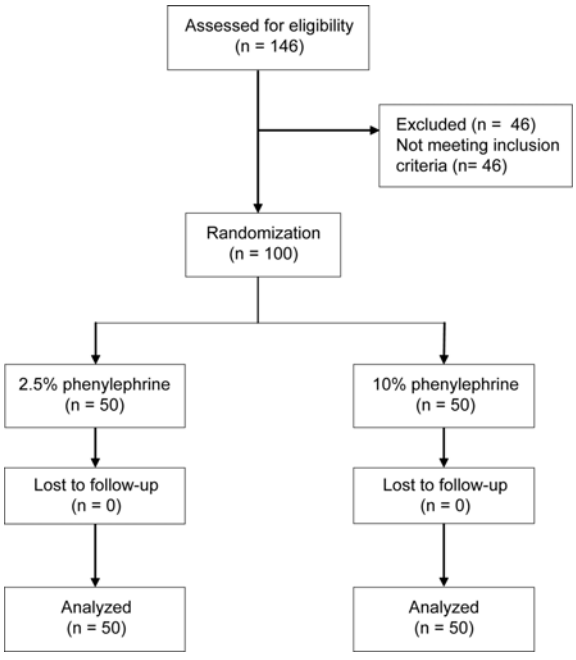

Fig. 1 Flow diagram of subject progress through the phases of a randomized trial

After initial visual acuity testing, applanation tonometry and slit-lamp biomicroscopy, all patients received one drop of 1% tropicamide in both eyes. After 30 minutes, either 2.5% or 10% phenylephrine was given to the patients by this research assistant. The digital images of the pupil were taken at 30 minutes after instillation of phenylephrine using automatic refractor Humphrey 598 (Humphrey System, Dublin, CA, USA), and the average pupil diameters were measured by image analysis program, Image-Pro Plus version 4.5 (Media Cybernetics, MD, USA) which automatically determined the dark area that corresponded to the pupil. After careful calibration, reliability of this procedure was repeatedly tested and it revealed good reproducibility.

Systemic side effects of phenylephrine were observed using automatic blood pressure monitor, Omron SEM-2 (Omron Healthcare Singapore LTD, UE Square, Singapore). Systolic blood pressure, diastolic blood pressure and heart rate were measured before and 30 minutes after phenylephrine instillation.

Statistical analysis

The SPSS for Windows version 11, SPSS Inc., Chicago, IL, USA) was used for data analysis. Independent t-test was carried out to determine efficacy of phenylephrine in different concentrations by comparing the mean pupil size and mean of difference in pupil size between the two groups. Furthermore, side effects of phenylephrine were also determined by comparing systolic and diastolic blood pressure and heart rate before and after drug instillation using paired t-test, while demographic characteristics were determined using Chi-square test. Statistical significance was taken as $p < 0.05$.

Results

Demographic data

The demographic data of the patients in both groups was shown in Table 1. Mean age of the patients was 54.2 $\pm$ 11.4 years and mean duration of diabetes was 89.9 $\pm$ 73.6 months, while mean fasting plasma glucose was 168.5 $\pm$ 56.8 mg/dl. Male and female ratio was 58:42. There was no statistically

significant difference in these data between the two groups ($p > 0.05$).

Pupil size

The mean pupil size at baseline and after instillation of tropicamide and phenylephrine in both concentrations are summarized in Table 2. The results showed that mean pupil sizes at baseline measurement were not statistically different between both groups. The patients aged below 60 years old had greater mean pupil size than the older patients with statistical significance (#1-4). After phenylephrine instillation, mean pupil sizes in 10% group were larger than those in the 2.5% group with statistical significance ($p = 0.02$). By using 10% concentration, mean pupil sizes of younger patients were larger than older patients with statistical significance (@3-4).

The age-mydriatic response correlations of each concentration were plotted in order to assess the pupil dilation effect in diabetic patients (Fig. 2). The results showed that the mydriatic response to 2.5% phenylephrine in diabetic patients was significantly correlated with patient's age ($r = 0.37$ and 0.36 on right and left eye respectively, p-value < 0.05). However, there was no correlation between mydriatic response and patient's age in 10% phenylephrine group ($r = 0.03$ and 0.07 on right and left eye respectively, p-value > 0.05). The mean of difference in pupil size after instillation phenylephrine was also shown in Table 2.

Table 1. Demographic data of the patients in both groups

Demographic data	10% phenylephrine	2.5% phenylephrine	p-value
Age (years)	54.9 ± 10.3	54.5 ± 12.5	0.81
Range (years)	21-78	28-75	
Patients (No.)	50	50	
< 60 years old	30	32	0.72
≥ 60 years old	20	18	0.85
Sex			
Female	30	28	
Male	20	22	
DM duration (months)	86.0 ± 75.8	93.7 ± 71.8	0.60
< 60 years old	91.4 ± 80.4	66.8 ± 58.5	0.13
≥ 60 years old	120.1 ± 98.1	97.2 ± 58.4	0.38
Fasting plasma glucose	166.9 ± 51.3	170.1 ± 62.3	0.78

Table 2. Pupil size at baseline, after instillation and mean of difference in pupil size in both groups

Pupil size (mm)	2.5% penylephrine		10% phenylephrine		p-value	
	RE	LE	RE	LE	RE	LE
Baseline	4.73 ± 1.09	4.66 ± 1.04	4.97 ± 0.94	4.87 ± 0.89	0.24	0.26
Age < 60	5.04 ± 1.10$^{\#1}$	4.93 ± 1.08$^{\#2}$	5.12 ± 0.82$^{\#3}$	5.00 ± 0.73$^{\#4}$	0.74	0.78
Age ≥ 60	4.26 ± 0.90$^{\#1}$	4.24 ± 0.85$^{\#2}$	4.49 ± 0.80$^{\#3}$	4.48 ± 0.80$^{\#4}$	0.40	0.40
After tropicamide	6.46 ± 0.74	6.45 ± 0.75	6.56 ± 0.78	6.60 ± 0.77	0.50	0.34
After phenylephrine	7.05 ± 0.71	7.05 ± 0.72	7.40 ± 0.72	7.39 ± 0.72	0.02	0.02
Age < 60	7.09 ± 0.61$^{@1}$	7.09 ± 0.66$^{@2}$	7.55 ± 0.70$^{@3}$	7.57 ± 0.66$^{@4}$	<0.01	<0.01
Age ≥ 60	7.00 ± 0.85$^{@1}$	6.98 ± 0.82$^{@2}$	7.12 ± 0.68$^{@3}$	7.07 ± 0.73$^{@4}$	0.63	0.71
Mean of difference	0.59 ± 0.45	0.59 ± 0.42	0.83 ± 0.40	0.79 ± 0.45	0.01	0.03
Age < 60	0.45 ± 0.39	0.45 ± 0.34	0.83 ± 0.39	0.79 ± 0.40	<0.01	<0.01
Age ≥ 60	0.81 ± 0.44	0.82 ± 0.45	0.83 ± 0.41	0.79 ± 0.53	>0.05	>0.05

#1–4 and @3-4: p-value < 0.05
@1-2: p-value > 0.05

Blood pressure and heart rate

There were no statistically significant differences in both mean systolic blood pressure and mean diastolic blood pressure between before and after instillation phenylephrine. However, the mean heart rate was increased with statistical significance after 10% phenylephrine instillation (Table 3).

Discussions

In this prospective randomized double-blind controlled trial, 10% phenylephrine appeared to be more effective than 2.5% phenylephrine for mydriasis in diabetic patients with darkly pigmented irides. This did not agree with previous reports that studied in lightly pigmented irides. Weiss et al [9] conducted a

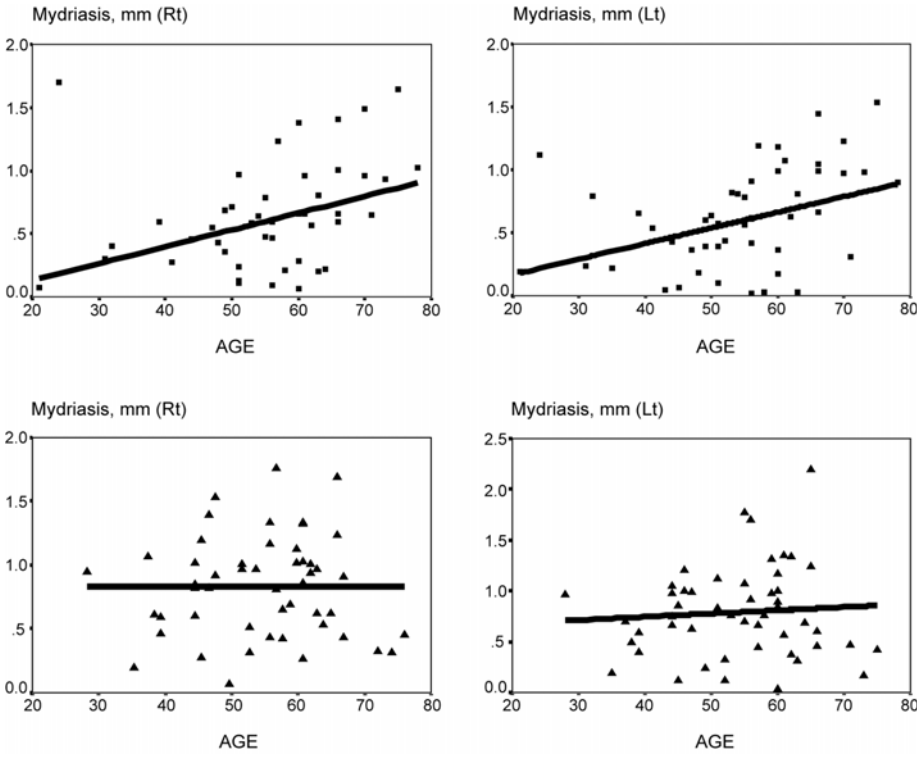

Fig. 2 Regression analysis between age and mydriatic effect of 2.5% (upper) and 10% (lower) phenylephrine. The difference in pupil size after 2.5% phenylephrine was correlated with age (r = 0.37 and 0.36, p-value < 0.01). The difference in pupil size after 10% phenylephrine was not correlated with age (r = 0.03 and 0.07, p-value = 0.985 and 0.615)

Table 3. Blood pressure and heart rate before and after phenylephrine instillation

BP and heart rate	Before	After	p-value
2.5% phenylephrine			
Systolic BP (mmHg)	124.66 ± 19.38	124.76 ± 19.12	0.95
Diastolic BP (mmHg)	71.50 ± 8.10	72.36 ± 8.33	0.32
Heart rate (bpm)	82.38 ± 12.54	81.36 ± 12.54	0.12
10% phenylephrine			
Systolic BP (mmHg)	127.76 ± 11.51	127.44 ± 14.66	0.83
Diastolic BP (mmHg)	76.38 ± 8.54	75.34 ± 9.41	0.37
Heart rate (bpm)	82.26 ± 11.05	84.74 ± 11.26	<0.01

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. Inan et al[10] also reported that the combination of 1% tropicamide and 2.5% phenylephrine was as effective as the combination of 1% tropicamide and 10% phenylephrine for mydriasis in diabetic patients with fewer systemic side-effects. However, the present study agrees well with previous reports that studied in healthy subjects with darkly pigmented irides[7,8]. These findings indicate that iris pigment plays an important role in mydriatic effect for both healthy subjects and diabetic patients.

Howard and Lee[11] 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. Angenent and Koelle[12] 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[13] 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 slower than in lightly pigmented irides which had thinner anterior layer and more numerous and larger crypts.

Interestingly, in the present study we found that the patients aged below 60 years old had greater mean baseline pupil size than the older patients with statistical significance. This might be attributed to iris degeneration resulting in increased iris rigidity[14] and accounted for the smaller pupil diameter at baseline measurement and limitation of maximum mydriatric effect in aging group.

The present study also demonstrated that the mydriatic response to 2.5% phenylephrine in diabetic patients with darkly pigmented irides was correlated with patient's age in contrast to those responses in 10% phenylephrine group. This age-dependent response pattern of 2.5% phenylephrine in pupil dilation was similar to the response in the healthy subjects[15]. The mechanism of this effect was supported by the evidence of pupillary supersensitivity to phenylephrine from sympathetic pupillary denervation in elderly people[16,17]. In diabetic patients, diabetic autonomic neuropathy is a well recognized complication[18] and pupillary autonomic denervation is regarded as an early sign of involvement of the autonomic nervous system[19,20]. This condition has an effect on the dilator muscle by affecting primarily the sympathetic nervous system and preserving parasympathetic system or sphincter muscle. Finally, it results in denervation supersensitivity to phenylephrine[15]. Therefore, age-dependent mydriatic response with 2.5% phenylephrine in diabetic patients with dark iris pigment may be attributed to the effect of denervation supersensitivity from both aging and diabetic autonomic neuropathy.

In contrast to the 2.5% phenylephrine result, the mydriatic response to 10% phenylephrine did not demonstrate any correlation with age. It might be due to denervation supersensitivity shifting the dose-response curve to the left, making the same dose cause much more change in reaction amplitude in the steep part of s-shaped dose-response curve[17,21], and eventually approaching the plateau part of maximum response curve when drug dosage is increased.

In the present study there was no statistically significant difference in the rise in blood pressure produced by both 2.5% and 10% phenylephrine. This agrees with all previous reports. Symons et al[22] reported no significant change in the mean systolic and diastolic blood pressure in patients receiving 10% phenylephrine. In addition, Malhotra et al[23] demonstrated no significant difference in the rise in blood pressure between the two groups. In the present study the mean heart rate after instillation in 10% phenylephrine group was greater than the value in 2.5% phenylephrine group with statistical significance. However, this is only by two or three beats per minute, which is not clinically significant.

Since the minimal pupil size for successful examination of the internal ocular structure is at least 6.5-7.0 mm[24,25]. The present study demonstrated that mean pupil diameters after both 2.5% and 10% phenylephrine were 7.05 ± 0.7 mm and 7.40 ± 0.7 mm respectively, which was sufficient for diabetic retinopathy screening. For this reason, the authors recommend a single dose of 10% concentration for mydriasis in diabetic patients with darkly pigmented irides for the maximum effect[26]. However, the lower concentration is recommended for use in those who exhibit a higher prevalence of significant vascular

disease and autonomic dysfunction from diabetic autonomic neuropathy, and seem to be susceptible to severe adverse reaction of phenylephrine.

In conclusion, in diabetic patients with darkly pigmented irides, the combination of 1% tropicamide and 10% phenylephrine is more effective in pupillary dilation than the combination of 1% tropicamide and 2.5% phenylephrine with statistical significance. However, there is no statistically significant difference in both mean systolic and diastolic blood pressure and no clinical significant difference in mean heart rate. Although the present study is a well designed prospective randomized double blind controlled trial, there are some limitations in the interpretation of the results such as exploratory post hoc analysis on the age-mydriatric response. Future research studies on this issue should be further investigated to confirm this correlation.

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Phenylephrine 2.5 % และ 10% ในการขยายรูม่านตาผู้ป่วยเบาหวานที่มีม่านตาสีเข้ม

โอฬาร สุวรรณอภิชน, ธนภัทร รัตนภากร, รณกร ปัญจพงศ์, สุธาสินี สีนะวัฒน์, ธรรศ สงวนศักดิ์, ยศอนันต์ ยศไพบูลย์

วัตถุประสงค์*: เพื่อเปรียบเทียบประสิทธิภาพ และผลข้างเคียงของยาหยอดตา phenylephrine 2.5% และ 10% ในการขยายรูม่านตาผู้ป่วยเบาหวานที่มีม่านตาสีเข้ม*

วัสดุและวิธีการ*: ผู้ป่วยเบาหวาน 100 ราย ได้รับการสุ่มแบบปิดสองทางเป็น 2 กลุ่ม กลุ่มที่ 1 ได้รับยาหยอดตา phenylephrine 2.5% กลุ่มที่ 2 ได้รับยาหยอดตา phenylephrine 10% ตรวจประเมินขนาดของรูม่านตา, ความดันโลหิต และชีพจรทั้งก่อนและหลังการหยอดยา*

ผลการศึกษา*: ขนาดรูม่านตาเฉลี่ยหลังหยอดตาในตาขวาเท่ากับ 7.05 $\pm$ 0.71 มม. ในกลุ่มที่ 1 และ 7.40 $\pm$ 0.72 มม. ในกลุ่มที่ 2 (p = 0.02) ในตาซ้าย เท่ากับ 7.05 $\pm$ 0.72 มม. ในกลุ่มที่ 1 และ 7.39 $\pm$ 0.72 มม. ในกลุ่มที่ 2 (p = 0.02) การตรวจประเมินความดันโลหิตและชีพจรไม่พบความแตกต่างระหว่าง 2 กลุ่มอย่างมีนัยสำคัญ*

สรุป*: ในผู้ป่วยเบาหวานที่มีม่านตาสีเข้ม ยาหยอดตา phenylephrine 10% มีประสิทธิภาพในการขยายรูม่านตาได้ดีกว่า 2.5% อย่างมีนัยสำคัญทางสถิติจึงแนะนำให้ใช้ยาหยอดตาขนาด 10% ในผู้ป่วยเบาหวานที่มีม่านตาสีเข้ม แต่แนะนำให้ใช้ยาหยอดตาขนาด 2.5% ในผู้ป่วยที่มีโรคของหลอดเลือดและมีความเสี่ยงต่อการเกิดผลข้างเคียงจากยาหยอดตา phenylephrine*