

## นิพนธ์ต้นฉบับ (Original Article)

### การเปรียบเทียบรูปแบบการหยอดยาขยายม่านตาผู้ป่วยเบาหวานด้วยยาหยอดผสมโทรปิคาไมด์ และฟีนิลเอฟรีน 4 วิธี: การศึกษาทางคลินิกแบบสุ่ม

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#### บทคัดย่อ

**บทนำ** การขยายม่านตาเป็นขั้นตอนสำคัญในการตรวจตา ม่านตาของผู้ป่วยเบาหวานอาจขยายได้ยากและต้องหยอดยาหลายครั้ง เนื่องจากระบบประสาทอัตโนมัติทำงานผิดปกติ

**วัตถุประสงค์** เพื่อเปรียบเทียบประสิทธิภาพและความปลอดภัยของการหยอดยา 4 รูปแบบ ในการขยายม่านตาผู้ป่วยเบาหวาน ด้วยยาผสม 0.8% tropicamide และ 5% phenylephrine

**วิธีการศึกษา** การศึกษาแบบสุ่มมีกลุ่มควบคุมในผู้ป่วยเบาหวาน 84 ราย (168 ตา) โดยสุ่มให้ตาทั้งสองข้างของแต่ละคนได้รับยาขยายม่านตา 1 หยด หรือ 3 หยด และสุ่มตาหนึ่งข้างของแต่ละคนให้ได้รับยา 0.5% tetracaine ก่อนขยายม่านตา ส่วนตาอีกข้างได้รับเพียงยาขยายม่านตา โดยวัดขนาดม่านตา ความดันโลหิต และชีพจร ก่อนและหลังหยอดยา 10, 20 และ 30 นาที

**ผลการศึกษา** การหยอดยาทั้ง 4 รูปแบบ (กลุ่มละ 42 ตา) ทำให้ม่านตาขยายได้ไม่แตกต่างกันอย่างมีนัยสำคัญ ( $p=0.901$ ) ปัจจัยที่มีผลต่อการขยายม่านตา คือปฏิสัมพันธ์ระหว่างเวลากับอายุ ( $p<0.001$ ) และเวลากับเพศ ( $p<0.001$ ) โดยม่านตาของผู้ที่อายุมากกว่า 70 ปีขยายน้อยกว่ากลุ่มอื่น และในนาที่ที่ 10 ม่านตาของผู้หญิงขยายมากกว่าผู้ชาย ทั้งนี้ทุกกลุ่มมีอัตราการขยายม่านตาสำเร็จ ( $\geq 6$  มิลลิเมตร) มากกว่าร้อยละ 80 นอกจากนี้การวัดขนาดม่านตาในนาที่ที่ 20 ทำนายการขยายม่านตาสำเร็จได้แม่นยำ (area under the receiver operating characteristic curve=0.935) ในแง่ความปลอดภัย ความดันโลหิตของทุกกลุ่มคงที่ ( $p\geq 0.140$ ) อย่างไรก็ตามกลุ่มที่ไม่เป็นความดันโลหิตสูงชีพจรเต้นช้าลง 5.1 ครั้งต่อนาที ( $p=0.004$ )

**สรุป** การหยอดยาขยายม่านตาเพียง 1 หยด ปลอดภัยและมีประสิทธิภาพในการขยายม่านตาผู้ป่วยเบาหวาน และการวัดขนาดม่านตาในนาที่ที่ 20 ช่วยระบุผู้ที่ม่านตาขยายช้าเพื่อหยอดยาเพิ่มได้ ทำให้บริหารจัดการผู้ป่วยได้ดีขึ้น

**คำสำคัญ** การขยายม่านตา การหยอดยา จอประสาทตาเบาหวาน ม่านตา ยาชา

#### ผู้นิพนธ์ที่รับผิดชอบ

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## Comparison of mydriatic effects between 4 regimens of a tropicamide-phenylephrine combination in diabetic patients: a randomized clinical trial

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### Abstract

**Introduction:** Pupillary dilation is essential for eye examination and surgery, but longstanding diabetes affects autonomic nervous responses. Pupillary dilation in diabetic patients may require repeated mydriatic drops to achieve adequate pupillary size.

**Objective:** To determine the most efficient method of a 0.8% tropicamide – 5% phenylephrine combination administration for pupillary dilation in diabetic patients.

**Methods:** This prospective randomized controlled study compared the efficacy and safety of four mydriatic regimens applied to 84 diabetic patients (168 eyes) scheduled for retinopathy screening. Both eyes of each patient received either one or three mydriatic drops, with one eye randomly assigned to receive antecedent 0.5% tetracaine. Pupillary size, blood pressure, and pulse rate were measured at baseline, and 10-, 20-, and 30-minutes post-administration.

**Results:** Repeated measures analysis of variance revealed no significant difference in pupillary dilation between each administration group of 42 eyes ( $p=0.901$ ). Significant interactions were observed for time  $\times$  sex ( $p<0.001$ ) and time  $\times$  age ( $p<0.001$ ). Women exhibited faster initial dilation at minute 10, while patients over 70 years achieved smaller final diameters. Over 80% of eyes in each group reached the clinical success threshold ( $\geq 6$  mm) by 30 minutes. Measurement at minute 20 was a highly accurate predictor of final success (area under the receiver operating characteristic curve=0.935). Systemically, blood pressure remained stable ( $p\geq 0.140$ ) in all groups, but a pulse rate reduction (5.1 beats/min) only occurred in non-hypertensive cohort ( $p=0.004$ ).

**Conclusions:** A single-drop regimen is equally effective and safe for diabetic patients. Implementing a 5-mm check at minute 20 can efficiently identify slow dilators requiring additional intervention, thereby optimizing outpatient workflow.

**Keywords:** Anesthetics, Diabetic retinopathy, Dilatation, Pupil, Topical administration

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## Introduction

Pupillary dilation is essential for ophthalmic practice, including comprehensive eye examinations in many conditions, cataract and vitreoretinal surgeries, and post-operative evaluations. The physiological regulation of pupillary size involves a balance between the dilator muscle ( $\alpha_1$ -adrenergic stimulation) and the sphincter muscle (muscarinic cholinergic action). Clinical mydriasis is typically attained using muscarinic antagonists, such as tropicamide, and/or  $\alpha_1$ -adrenergic agonists, such as phenylephrine.

However, achieving effective dilation in diabetic patients presents unique challenges. Longstanding diabetes is negatively correlated with pupillary size and dilation due to abnormal autonomic nervous responses.<sup>1-8</sup> Furthermore, standard clinical protocols often require repeated eye drops,<sup>6, 9-14</sup> which can cause dissatisfaction among waiting patients in a crowded clinic. To optimize this process, topical anesthetics like tetracaine are sometimes used, as they theoretically increase the corneal penetration of mydriatic agents and decrease reflex tear production from mydriatic drops. While some studies suggested topical anesthetics enhanced mydriasis and patient comfort,<sup>9-11</sup> others reported no significant difference.<sup>12</sup> There remains limited data comparing the efficacy of single-drop versus multiple-drop regimens using a 0.8% tropicamide – 5% phenylephrine combination in diabetic populations.

## Objective

This study aims to determine which administration method provides sufficient pupillary dilation by comparing four distinct protocols involving variations in the number of mydriatic drops and the use of prior anesthetics.

## Methods

### Population and Sampling

This prospective, single-blind, randomized controlled study conducted at the Ophthalmology Outpatient Department, Burapha University Hospital, Chonburi, Thailand. The study proceeded between November 2024 to January 2025.

### Inclusion Criteria

Diabetic patients, aged 18 years or older, scheduled for diabetic retinopathy screening in Burapha University Hospital, Chonburi, Thailand.

### Exclusion Criteria

Excluded were patients with one of the following statuses.

1. Conditions potentially affecting pupillary reaction (e.g., history of uveitis, previous intraocular surgery, posterior synechiae, pseudoexfoliation)
2. Conditions potentially affecting the measurement of pupillary size (e.g. corneal haziness)
3. Narrow anterior chamber angle (Van Herick Grade 0-2)
4. Known allergies to study medications

5. Systolic blood pressure (SBP) > 160 mmHg
6. Diastolic blood pressure (DBP) > 100 mmHg
7. Pulse rate (PR) > 100 beats/min
- mydriatic drug, while the fellow eye did not. This resulted in four parallel treatment groups.
- Group 1: one mydriatic drop
- Group 2: one tetracaine drop + one mydriatic drop
- Group 3: three mydriatic drops
- Group 4: one tetracaine drop + three mydriatic drops

### Material Research

The sample size for this study was calculated a priori to ensure sufficient statistical power to detect differences between the four administration regimens. Using a significance level ( $\alpha$ ) of 0.05, a power of 0.80, and a large effect size, the minimum required sample size was determined to be 76 patients. To account for a potential 10% dropout rate, the final enrollment target was set at 84 patients, providing a total of 168 eyes for analysis. This calculation was performed to validate that the study could effectively compare the efficacy and safety of the 0.8% tropicamide and 5% phenylephrine combination across the four parallel treatment groups.

This study utilized a commercially available fixed-combination eye drop containing 0.8% tropicamide and 5% phenylephrine (Mydriamac; Maxim, Thailand) as the mydriatic drug. The topical anesthetic was 0.5% tetracaine hydrochloride (Alcon Laboratories, Inc., Fort Worth, TX, USA). Each patient was randomized to receive either one drop or three drops (one drop, administered 3 times, 5 minutes apart) of the mydriatic combination. And one eye of each patient was randomly assigned to receive one drop of 0.5% tetracaine 30 seconds before the

Group 1 and 2 were from the same patients. Group 3 and 4 were also from the same patients.

The randomization process was conducted through a single-step simple random drawing by the principal investigator prior to recruitment. Each patient was assigned once to one of four predefined configurations (A, B, C, or D) in balanced blocks of four to ensure equal distribution across the four regimens. This single randomization determined both the number of mydriatic drops (1 vs. 3) and the side (right vs. left eye) assigned to receive the antecedent topical anesthetic.

A: right eye = group 1, left eye = group 2.

B: right eye = group 2, left eye = group 1.

C: right eye = group 3, left eye = group 4.

D: right eye = group 4, left eye = group 3.

The allocation sequence was stored securely on a password-protected computer. To maintain blinding, the principal investigator administered the medication to all patients out of sight of the assessor.

### Data Collection

Baseline pupillary size was measured using a slit lamp ophthalmoscope (0.5 mm slit beam width, 10x magnification) in normal room illumination by one blinded ophthalmologist. The smallest pupillary size following direct light reflex (if any) was recorded in vertical and horizontal diameters. Following the administration of the assigned topical medications, patients were asked to close their eyes for one minute. Pupillary diameter was then re-evaluated at 10, 20, and 30 minutes using the same method by the same blinded ophthalmologist. Systemic safety was monitored via SBP, DBP, and PR at every pupillary measurement interval. Ocular discomfort was reported, as a pain score of 0-10 with the increment of 1, upon the conclusion of all measurements to assess the tolerability of each method. During the 30-minute period, each patient was requested to rest on a chair in silence.

### Data Analysis

The primary analysis employed a repeated measures analysis of variance (ANOVA) to determine the effects of the administration method (between-subjects factor) and time

(within-subjects factor) on the average of vertical and horizontal pupillary diameters. Given that the study included both eyes of each patient, a linear mixed-effects model was used to evaluate the intraclass correlation coefficient (ICC) to account for inter-eye correlation. Baseline characteristics, including age, sex, and duration of diabetes, were analyzed for their impact on the results. All safety outcomes were evaluated by Brunner-Munzel test. The statistics were analyzed using Jamovi, version 2.6.44 for Windows (The Jamovi Project, Sydney, Australia).

### Ethical Consideration

Ethical clearance was approved from full board review by the Institutional Ethical Committee (IRB1-052/2567) on 27<sup>th</sup> May 2024. All clinical procedures adhered to the Declaration of Helsinki. Written informed consent was collected from all patients after acknowledging the details of the study.

### Results

There were 84 participants enrolled in this study with no dropouts, resulting in a total of 168 eyes across four parallel treatment groups (42 eyes per group). Their baseline characteristics, including diabetes duration and hypertensive status were shown by group (Table 1).

**Table 1** Baseline characteristics of study participants

| Baseline Characteristics                | Mydriatic Drug  |                | Total          | p-value |
|-----------------------------------------|-----------------|----------------|----------------|---------|
|                                         | 1 drop (n=42)   | 3 drops (n=42) |                |         |
| Age (years), mean±SD                    | 59.3±12.8       | 56.8±18.6      | 58.0±15.9      | 0.478   |
| Sex (female), n (%)                     | 27 (64.3)       | 31 (73.8)      | 58 (69.0)      | 0.345   |
| Diabetes duration (years), median (IQR) | 5.0 (1.25-10.0) | 7.0 (1.0-15.0) | 5.0 (1.0-12.8) | 0.277   |
| Hypertension, n (%)                     | 33 (78.6)       | 23 (54.8)      | 56 (66.7)      | 0.021*  |

**Note:** \*=statistical significance ( $p < 0.05$ ), IQR=interquartile range, n=number of participants, SD=standard deviation

From Table 1, the age of the participants was between 19 and 88 years. The average age (mean  $\pm$  standard deviation) was  $58.0 \pm 15.9$ . Of these, 58 (69.0%) were female. The median diabetes duration was 5 years (interquartile range = 1.0-12.8). Although they were randomized, a Chi-square analysis revealed a baseline imbalance in the prevalence of hypertension between the group receiving 1-drop and 3-drop of mydriatic drug ( $p = 0.021$ ).

Consequently, safety analyses included subgroup adjustments to ensure whether any

observed variances in the vital signs were attributable to pre-existing conditions or the study intervention. There were no statistically significant differences in baseline pupillary diameters among the groups ( $p = 0.164$ ). The mean pupillary sizes (in millimeters  $\pm$  SD) for group 1, 2, 3, and 4 were  $2.62 \pm 0.332$ ,  $2.65 \pm 0.331$ ,  $2.50 \pm 0.437$ , and  $2.51 \pm 0.441$ , respectively.

The major results of repeated measures ANOVA were shown below (Table 2).

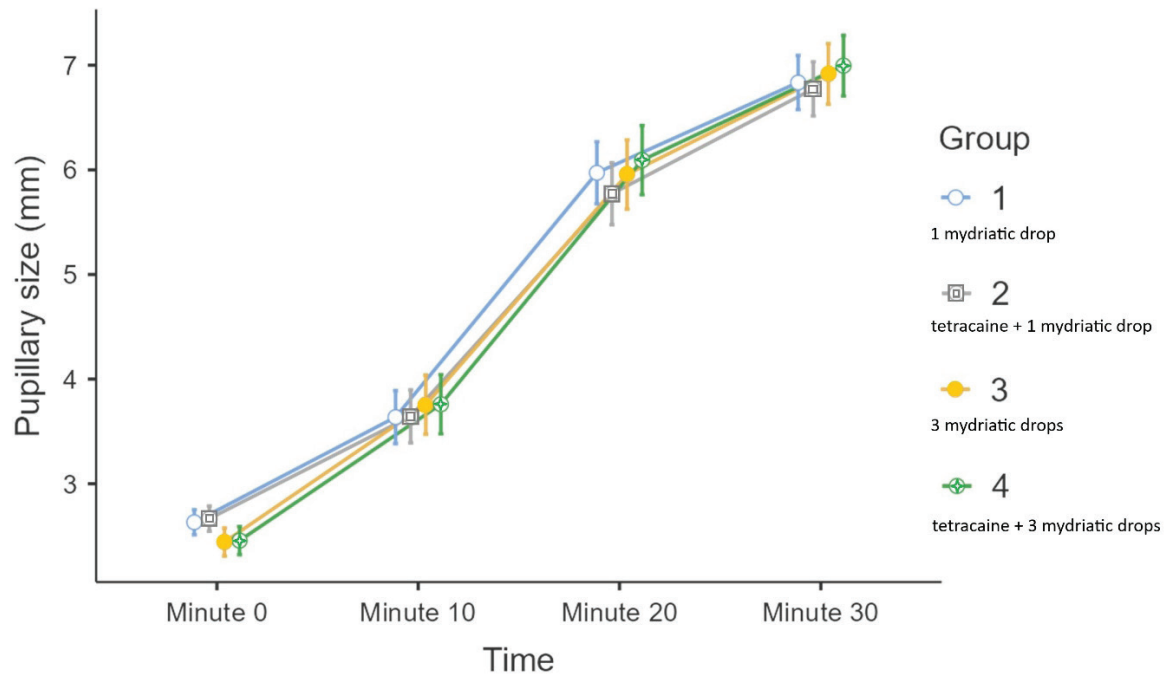
**Table 2** Repeated measures analysis of variance for pupillary size

| Source of variation | F-statistic | df   | p-value |
|---------------------|-------------|------|---------|
| Time                | 199.924     | 2.49 | <0.001* |
| Time $\times$ Age   | 11.391      | 2.49 | <0.001* |
| Time $\times$ Sex   | 8.052       | 2.49 | <0.001* |
| Group               | 0.193       | 3    | 0.901   |
| Eye                 | 0.350       | 1    | 0.555   |

**Note:** Greenhouse-Geisser corrections applied for non-sphericity.

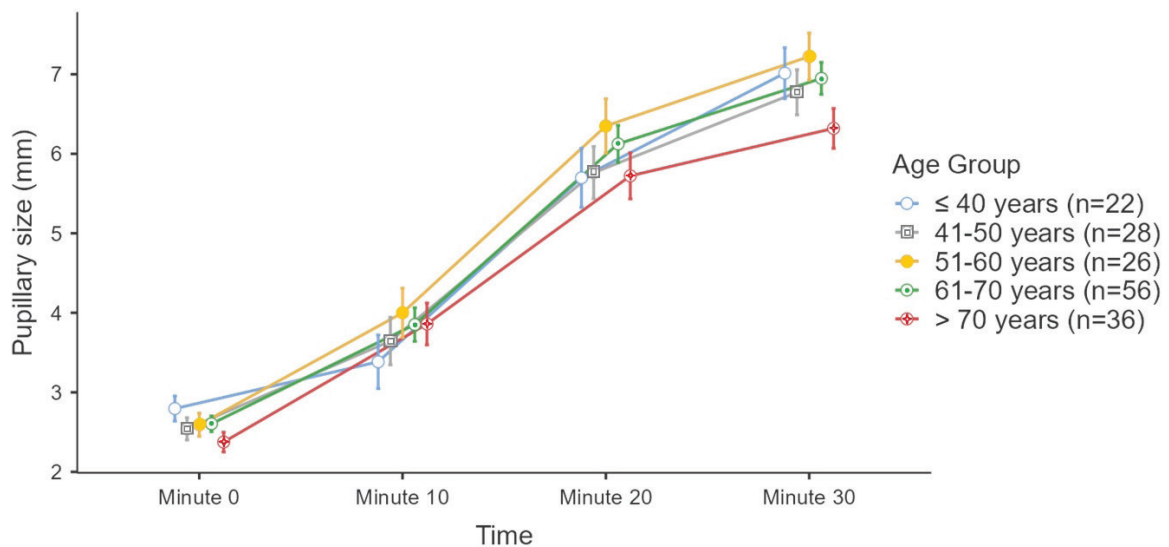
\*=statistical significance ( $p < 0.05$ ), df = degrees of freedom, DM = diabetes mellitus

Table 2 revealed that significant factors influencing pupillary size were time, time × age interaction, and time × sex interaction. Pupillary diameters at each time point for each treatment group and age group were shown in Figure 1 and 2, respectively.



**Figure 1** Mean pupillary dilation over 30 minutes for four treatment groups. No significant difference in efficacy was observed between regimens ( $p=0.901$ ). Error bars represented confidence interval.

Figure 1 showed that pupillary diameter increased without significant difference in all treatment groups ( $p = 0.901$ ).



**Figure 2** Pupillary dilation dynamics (at minute 0, 10, 20 and minute 30) by age group. Error bars represented confidence interval.

From Figure 2, one-way ANOVA and Tukey's honestly significant difference test found that patients with age of more than 70 years had smaller final pupillary size than other groups (except 41-50 years). The > 70 years group showed significant mean differences compared to the  $\leq 40$  years ( $-0.69$  mm,  $p = 0.008$ ), 51-60 years ( $-0.90$  mm,  $p < 0.001$ ), and 61-70 years ( $-0.63$  mm,  $p = 0.002$ ) cohorts.

Women exhibited significantly larger pupils at minute 10 than men ( $3.92$  vs  $3.46$  mm,  $p < 0.001$ ), although final pupillary diameters were comparable ( $6.80$  vs  $6.90$  mm,  $p = 0.466$ ) by two-sample t-test. Neither the main effect of diabetes duration nor its interaction with time reached statistical significance. The ICC for pupillary diameter was  $0.968$ , indicating excellent inter-eye correlation. This dependency was statistically accounted for, which is consistent with the

finding that the "eye" factor had no significant main effect on the results ( $p = 0.555$ ).

Since pupillary diameter of  $6$  mm is generally accepted for peripheral retina examination,<sup>13-16</sup> Chi-square test revealed no significant difference in clinically successful dilation between administration groups ( $p = 0.594$ ). All groups had over  $80\%$  of eyes with successful dilation. Further analysis showed that eyes with final pupils not reaching  $6$  mm had significantly smaller pupils at minute 20 than the successful dilation group by two-sample t-test ( $4.71$  vs  $6.20$  mm,  $p < 0.001$ ). A pupillary check at minute 20 was found to be a highly accurate predictor of final success with area under the curve from receiver operating characteristic (ROC) analysis of  $0.935$  (95% confidence interval =  $0.899$ - $0.970$ ).

Systemic safety evaluation was demonstrated in Table 3, with hypertensive status being included in the ANOVA.

**Table 3** Systemic safety profiles at each time point

| Vital Signs  | Time Point (minute) |           |           |           | <i>p</i> -value <sup>a</sup> | <i>p</i> -value <sup>b</sup> |
|--------------|---------------------|-----------|-----------|-----------|------------------------------|------------------------------|
|              | 0                   | 10        | 20        | 30        |                              |                              |
| SBP (mmHg)   | 145±12.3            | 145±16.0  | 144±14.7  | 145±15.1  | 0.611                        | 0.730                        |
| DBP (mmHg)   | 84.0±9.01           | 82.6±9.32 | 82.9±10.2 | 83.0±9.89 | 0.140                        | 0.405                        |
| PR (bpm)     | 82.5±11.5           | 81.3±11.7 | 79.9±11.9 | 80.3±11.8 | <0.001*                      | 0.790                        |
| PR (bpm)     |                     |           |           |           |                              |                              |
| non-HT group | 84.0±9.30           | 80.1±10.0 | 79.0±9.99 | 79.7±10.4 | 0.004* <sup>c</sup>          |                              |
| HT group     | 81.8±12.4           | 81.9±12.4 | 80.3±12.7 | 80.6±12.5 | ≥0.422                       |                              |

**Note:** Data presented as mean±standard deviation. Greenhouse-Geisser correction applied for SBP due to non-sphericity ( $p=0.029$ ). \*=statistical significance ( $p<0.05$ ), a=within-subjects effect, b=interaction between time with administration group, c=between minute 0 and 20, bpm=beats per minute, DBP=diastolic blood pressure, HT=hypertensive, PR=pulse rate, SBP=systolic blood pressure

Table 3 demonstrated that mean SBP and DBP remained stable throughout the study without significant main effect for time ( $p = 0.611$  and  $p = 0.140$ , respectively) or interaction between time and administration group ( $p = 0.730$  and  $p = 0.405$ , respectively). A decrease in PR over time was observed ( $p < 0.001$ ).

Subgroup analyses of blood pressure revealed that hypertensive patients maintained a higher SBP level compared to non-hypertensive patients ( $p = 0.003$ ). Despite time  $\times$  hypertensive status interaction being significant for DBP ( $p = 0.041$ ), post-hoc pairwise comparisons showed no significant differences between each time point and group ( $p \geq 0.067$  for all comparisons). PR reduction was without significant interaction between time and administration group ( $p = 0.790$ ). However, significant time  $\times$  hypertensive status interaction for PR was noticed ( $p = 0.047$ ). Post-hoc comparisons revealed that PR reduction was only apparent in non-hypertensive cohort, most notably during minute 0 to 20 (5.1 beats/min,  $p = 0.004$ ). Ocular discomfort scores had no significant difference between groups ( $p = 0.070$ ) with median score of 2 (interquartile range = 1-3). Unintended events did not appear during the study.

## Discussion

The primary finding that a single-drop regimen is as effective as multiple drops aligns with finding by Roy et al, suggesting that simplified protocols can significantly

reduce clinical workload and financial burdens in resource-limited countries without compromising the efficacy.<sup>17</sup> Previous studies reported smaller dilated pupillary size<sup>4-6</sup> or longer period until maximal pupillary diameter<sup>18</sup> in longstanding diabetes or diabetes with more severe retinopathy; however, most of them applied either tropicamide or phenylephrine or alternating drops between these medications. Many authors indicated that a combination of muscarinic antagonist and  $\alpha_1$ -adrenergic agonist was superior to either one of them,<sup>11, 13, 15, 19-23</sup> and did not require high concentration of phenylephrine<sup>24</sup> in order to prevent possible systemic side effects.<sup>25</sup> In our study, diabetes duration was subgrouped by multiple duration cut-off, but no significant difference between groups was found.

A key clinical contribution of this study is the validation of the minute 20 check. Based on ROC analysis and optimal cut-off selection using 0.5-mm increments for practical clinical application, a 5-mm cut-off had the highest accuracy (88.1%). Eyes reaching this threshold at minute 20 will generally be ready for examination 10 minutes later, whereas those falling below the threshold should be considered for an immediate rescue drop to facilitate the clinic workflow.

Regarding safety, the mydriasis was well tolerated, as there were no significant changes in mean SBP or DBP over the study period, similar to many previous studies.<sup>17, 19, 20, 24, 26</sup> Although, some authors reported

an increase in SBP with the use of higher concentration of phenylephrine.<sup>27-29</sup> Our subgroup analyses confirmed that blood pressure variability was driven by pre-existing hypertension rather than the drug itself. A PR reduction of 5.1 beats/min in non-hypertensive patients may be accounted for by physiological reflex bradycardia from phenylephrine. The reflex, however, was of minimal impact on the hypertensive group, plausibly from the altered autonomic tone. In 1980, Brown et al also reported decreased PR with 1% tropicamide,<sup>26</sup> but thereafter, most other studies found it stable.<sup>11, 17, 19, 20, 24</sup> Collectively, these findings demonstrate that both single-drop and multiple-drop regimens are systemically safe for the diabetic population, including those with pre-existing hypertension.

Despite offering pragmatic clinical guidance, this study has several limitations. First, we only included patients scheduled for routine diabetic retinopathy screening. Patients with more advanced stages of the disease (e.g., severe nonproliferative diabetic retinopathy or diabetic macular edema) are typically managed directly by an ophthalmologist and are excluded from the standard screening registry. Consequently, our findings may not be generalizable to this more severe cohort. Second, blood glucose levels during the dilation period may influence the extent of pupillary expansion, even though abnormal autonomic nervous responses are not thought to fluctuate acutely. Future studies should consider measuring blood glucose or glycated

hemoglobin on the day of pupillary dilation. Third, manually measuring pupillary size with a slit lamp required approximately 30 seconds per eye, meaning the pupil of the fellow eye may have continued to dilate during that interval. Nonetheless, this confounding effect was likely negligible because the anesthetic drop was randomly assigned to either eye, whereas the right eye was always measured first. Utilizing advanced pupillometry instruments that provide high-resolution data within seconds would eliminate this potential confounder. It would also allow for more frequent interval of pupillary assessment, enabling the use of a Cox proportional hazards model to evaluate the velocity of clinical success. Fourth, while ocular discomfort was assessed globally in this study, evaluating it on a per-eye basis in future research may provide more granular information regarding local tolerability.

## Conclusion

One drop of a 0.8% tropicamide - 5% phenylephrine combination is as effective and safe as more intensive protocols for dilating diabetic patients undergoing eye examinations. Implementing a 5-mm check at minute 20 will ensure patient readiness and identify slow dilators who may require additional intervention.

## New Knowledge

1. Topical administration of a 0.8% tropicamide – 5% phenylephrine combination

for one drop is enough and safe for adequate pupillary dilation for retina examination even in diabetic or hypertensive patients. However, preoperative pupillary dilation may still require repeated topical administration for full dilation.

2. Pupillary size checking at 20 minutes after applying mydriatic drop can identify slow dilators, whose pupillary size is still less than 5 mm, and may require additional intervention for achieving adequate pupillary dilation.

### Suggestion

Pupillary dilation in a hospital (outpatient and inpatient department) for retina examination can be achieved with one drop of a 0.8% tropicamide – 5% phenylephrine combination.

### Acknowledgement

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### References

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