Original Article

Efficacy of A Mydriatic Mixture of 0.5% Tropicamide and 5% Phenylephrine at Thammasat University Hospital

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Abstract

Purpose: To compare the effectiveness of mydriasis between mydriatic mixtures of 0.5% tropicamide and 5% phenylephrine versus 1% tropicamide and 10% phenylephrine.

Design: Prospective randomized controlled trial

Methods: In this study, 30 Asian patients with dark irides were randomized to receive topical 1% tropicamide and 10% phenylephrine (conventional regimen), and 30 patients to receive a fixed combination of 0.5% tropicamide and 5% phenylephrine (mixed regimen). The vertical pupillary dilatation, blood pressure, and pulses were studied.

Results: Sixty patients were equally randomized into conventional and mixed regimens. For the conventional and mixed regimen groups; the mean baseline pupil diameter was 1.49 ± 0.62 mm and 1.84 ± 0.64 mm, respectively. The mean pupil diameter at 15 minutes was statistically significant difference between both groups, 3.79 ± 0.90 mm in the conventional regimen group and 4.30 ± 1.05 mm in the mixed regimen group with mean difference 0.5133 mm (95%CI 0.0076 - 1.0191, P = 0.047). Whereas the mean pupil diameter at 30, 45, and 60 minutes showed no significant difference between groups. In the first 30 minutes, the proportion of eyes that achieved 7 mm pupil size between both groups was significant difference, 36.7% in the conventional regimen group, and 63.3% mixed regimen group (P=0.039). At 60 minutes, the proportion was 86.7% and 96.7% respectively (P = 0.353). There was no significant difference in arterial blood pressure and pulse rate between groups.

Conclusion: The mixture of 0.5% tropicamide and 5% phenylephrine showed comparable efficacy to a conventional regimen and resulted in greater pupillary dilatation within the first 15 minutes, allowing for more rapid achievement of desired mydriasis.

Keywords: Mydriatics, Phenylephrine, Tropicamide, Pupillary dilatation

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Introduction

In order to obtain adequate fundus examination, pupils need to be dilated by mydriatics. Pupils are innervated by both parasympathetic and sympathetic innervations. Pupil dilatation is routinely use 1% tropicamide and 10% phenylephrine.[1] Also in our outpatient clinic, the conventional regimen uses 1% tropicamide and 10% phenylephrine instillation alternately every 5 minutes for 4 times. Tropicamide, an antimuscarinic agent, produces side effect of cycloplegia. Phenylephrine, alpha-adrenergic agonist, has systemic side effects include a rise in blood pressure, tachycardia, reflex bradycardia, headache. Both mydriatics have side effects of blurred vision, stinging sensation, redness and corneal punctate epithelial erosion. The side effects most relate with dosage.[2]

The mydriatics for eye examination need adequate dilatation, rapid onset, and minimal side effects. A fixed combination of tropicamide and phenylephrine might reduce side effects, less uncomfortable and decrease workloads in outpatient clinic setting. Although, many previous studies of mydriatic mixtures, which composed of 1.25% or 2.5% phenylephrine, aimed to avoid as much as possible unfavorable effects. Obianwu et al reported light irides more response to ephredine than dark irides.[3] Yospaiboon et al studied mydriatic effect of 2.5% and 10% phenylephrine in dark irides. The studies showed superior efficacy in higher concentration of phenylephrine.[4] This randomized controlled trial intends to distinctively compare efficacy and side effects of a mydriatic mixture of 0.5% tropicamide and 5% phenylephrine with fewer drops to conventional regimen.

Methods

This prospective randomized controlled trial was approved by Ethics Committee of the Faculty of Medicine, Thammasat University, Thailand in accordance with the declaration of Helsinki (MTU-EC-OP-1-018/62). Written informed consents were obtained from eligible patients before the study began. The inclusion criteria were Asians with dark iris patients at Ophthalmology Clinic of Thammasat University Hospital who requiring pupillary dilatation and rage in age from 18 to 80 years old. Exclusion criteria included those with a history of underlying diseases of diabetes mellitus, uncontrolled systemic hypertension and cardiovascular disease. Those patients with a history of allergy to mydriatics, previous medications that may affect pupil dilatation, intraocular surgery or laser treatment, ocular disease that affect pupil size were excluded such as glaucoma, uveitis, infectious eye diseases.

The sample size of 60 patients was calculated from hypothesis testing for non-inferiority analysis. The authors used the standard deviation of 0.8 from previous study.[5] At 95% confident level, a power of 80% and an acceptable pupil size difference of 0.6 mm, the required sample size was at least 22 for each group.

The dilating eye drops for conventional regimen composed of two commercial preparations; 1% tropicamide (Mydriacyl®, Alcon Laboratory, Thailand) and 10% phenylephrine (Phenylephrine Hydrochloride Ophthalmic Solution 10%®, Biolab Co., Ltd, Thailand) in separate bottles. The fixed combination of this mixed regimen was composed of those mydriatics in a ratio of 1:1. The mixed regimen was prepared under aseptic conditions from commercial preparations resulted in a concentration of 0.5% tropicamide and 5% phenylephrine in standard dropper bottles.

The patients were allocated by simple random sampling method and one eye was selected. In both sided pupil dilatation, the eye was selected by the date of enrollment. In even days, the right eye was selected. In odd days, the left eye was selected.

The patients in the conventional regimen group were instilled 1% tropicamide and then 10% phenylephrine alternately every 5 minutes for 4 times (at 0, 5, 10, 15 minutes). In mixed regimen group, they were instilled the mixed regimen every 5 minutes for 2 times (at 0, 5 minutes). Any other eye drops were not allowed. In both groups, the pupil diameters were vertically measured by slit lamp with 0.1 mm wide slit beam in maximum light intensity for baseline data and then every 15 minutes until 60 minutes. The goal of pupillary dilatation was at least 7 mm to achieve sufficient fundus examination.[1] The arterial blood pressure and pulses were measured by an automatic sphygmomanometer (Terumo Digital Blood Pressure Monitor ES-H55) for base line data and then every 30 minutes until 60 minutes.

The primary outcome was the differences of the mean pupillary diameters at 15, 30, 60 minutes and percentages of goal achievement of pupillary dilatation. The secondary outcomes were changes in systolic, diastolic arterial blood pressure and pulses.

A comparative analysis of continuous data was performed by an independent t-test in normative data and Mann-Whitney U test in non-nominal distribution. A comparative analysis of categorical data was performed by a Chi-square test. SPSS version 23 was used for these analyses. A *P* - value of 0.05 or less was considered statistically significant.

Results

Demographic data

Sixty patients participated in this study. Thirty-eight patients (63.3%) were female. The mean age was 60.1 ± 12 years (ranged from 25 to 80 years). The patients' demographic data is shown in Table 1. There was no statistically significant difference between two groups.

Table 1 Baseline demographic data

	Total (n = 60)		**Conventional (n = 30)**		**Mix (n = 30)**		***P* - value**
	n	**%**	**n**	**%**	**n**	**%**	
Sex							0.284
Female	38	63.3	21	70.0	17	56.7	
Male	22	36.7	9	30.0	13	43.3	
Age							0.577
< 60	20	33.3	9	30.0	11	36.7	
60-59	26	43.3	15	50.0	11	36.7	
≥ 70	14	23.3	6	20.0	8	26.7	
Mean ± SD	60.10 ± 12.90		61.27 ± 7.63		58.93 ± 16.65		0.865
Underlying							0.190
Yes	25	41.7	10	33.3	15	50.0	
No	35	58.3	20	66.7	15	50.0	
Hypertension	15	25.0	5	16.7	10	33.3	0.136
Dyslipidemia	4	6.7	2	6.7	2	6.7	1.000
Others	6	10.0	3	10.0	3	10.0	1.000

P - value from Chi-Square test, Fisher's Exact Test and Mann-Whitney U-test
*Significant at the 0.05 level

Primary outcome

The initial baseline mean pupil diameters for conventional regimen group and mixed regimen group were 1.49 ± 0.62 mm and 1.84 ± 0.64 mm respectively (P = 0.055). There was no significant difference between baseline pupil diameter. At 15 minutes, pupillary dilatations between both groups were statistically significant, the mean pupil diameter in the conventional regimen group was 3.79 ± 0.90 mm and in the mixed regimen group was 4.30 ± 1.05 mm with mean difference between groups 0.5133 (95% CI 0.0076-1.0191, P = 0.047) (Table 2, Figure 1). The mean pupil diameters at other time points in both groups were not statistically different, the mean pupil diameter in conventional regimen group versus mixed regimen group at 30, 45, 60 minutes were 6.55 ± 1.01 vs. 6.93 ± 0.97 mm (P = 0.118), 7.46 ± 0.83 vs. 7.65 ± 0.64 mm (P = 0.486) and 7.94 ± 0.95 vs. 8.10 ± 0.60 mm (P = 0.448) respectively. The mean difference of pupil diameters at 30, 45, 60 minutes were 0.3800 (95%CI -0.1319 - 0.8919), 0.1967 (95%CI - 0.1863 - 0.5797),

Table 2 Mean and mean differences of pupil sizes between the two group

	Total (n = 60)	Conventional (n = 30)	Mix (n = 30)	Mean Difference	Std.Error Difference	95% CI of the) Difference		*P* - value
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.			Lower	Upper	
Pupil 0 min	1.67 ± 0.65	1.49 ± 0.62	1.84 ± 0.64	0.3467	0.1626	0.0213	0.6721	0.055
Pupil 15 min	4.04 ± 1.00	3.79 ± 0.90	4.30 ± 1.05	0.5133	0.2527	0.0076	1.0191	0.047*
Pupil 30 min	6.74 ± 1.00	6.55 ± 1.01	6.93 ± 0.97	0.3800	0.2557	-0.1319	0.8919	0.118
Pupil 45 min	7.56 ± 0.74	7.46 ± 0.83	7.65 ± 0.64	0.1967	0.1913	-0.1863	0.5797	0.486
Pupil 60 min	8.02 ± 0.79	7.94 ± 0.95	8.10 ± 0.60	0.1567	0.2048	-0.2549	0.5683	0.448

P - value from Mann-Whitney U-test and Independent t-test

*Significant at the 0.05 level

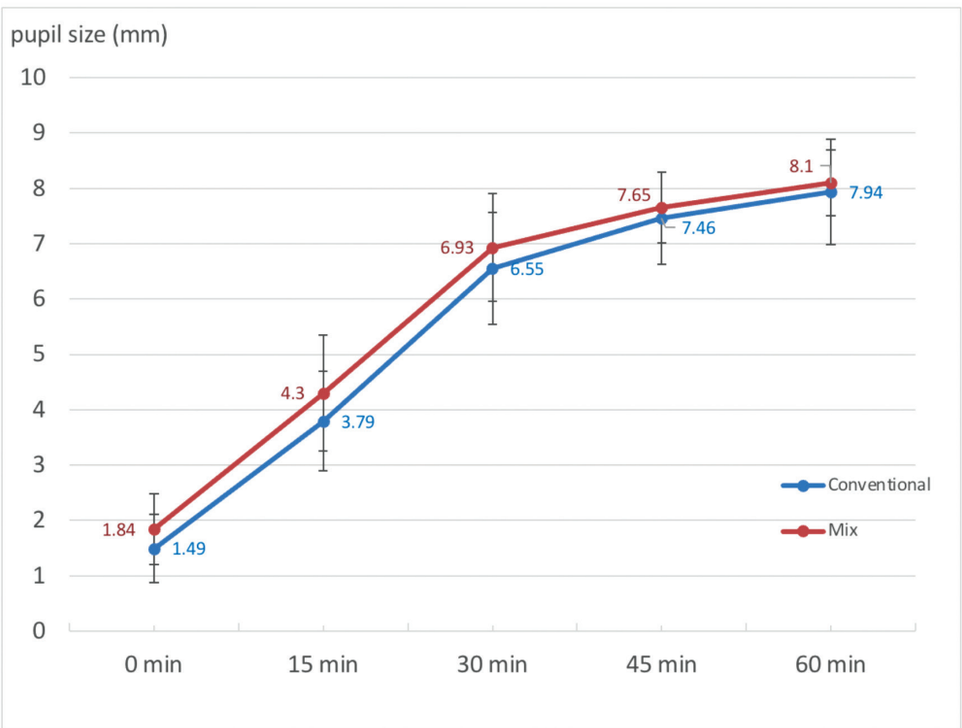

Figure 1 Mean pupil diameter at each time point.

0.1567 (95%CI -0.2549 - 0.5683) (Table 2, Figure 1). Within 30 minutes, the proportion of success of pupil dilatations to 7 mm for the conventional regimen group versus mixed regimen group were 36.7% versus 63.3%. The difference was statistically significant with *P* - value 0.039. However, within 60 minutes, the proportions between both groups were not statistically significant, 86.7% in conventional regimen group and 96.7% in mixed regimen group with *P*-value 0.353 (Table 3).

Table 3 Success of pupil dilatation to 7 mm

	Totle (n = 60)		**Conventional (n = 30)**		**Mix (n = 30)**		***P* - value**
	n	%	n	%	n	%	
Goal 30 min							0.039*
Yes	30	50.0	11	36.7	19	63.3	
No	30	50.0	19	63.3	11	36.7	
Goal 45 min							0.228
Yes	53	88.3	25	83.3	28	93.3	
No	7	11.7	5	16.7	2	6.7	
Goal 60 min							0.353
Yes	55	91.7	26	86.7	29	96.7	
No	5	8.3	4	13.3	1	3.3	

P - value from Chi-Square test and Fisher's Exact Test

* Significant at the 0.05 level

Secondary outcome

In this study, there was no significant difference between two groups for the arterial blood pressure and pulses. In both groups, mean systolic and diastolic blood pressure at 30, 60 minute showed statistically significant differences compared to base line data but not clinically significant. Mean pulses in both groups were statistically significant lower than pulses at 0 minute (Table 4).

Discussion

To complete eye examination, pupillary dilatation is a mandatory practice. Pupil diameter at least 7 mm allows adequate examination[1, 6] Pupil dilatation is controlled by autonomic regulation. The routine commercials available of mydriatics are 1% tropicamide and 10% phenylephrine. Tropicamide, an antimuscarinic agent, has iris sphincter inhibitory effect whereas phenylephrine was the iris dilator stimulation. These two mydriatics develop synergistic effect.[7]

In this prospective randomized clinical trial, we used a mixture of 0.5% tropicamide and 5% phenylephrine to compare with alternate application of 1% tropicamide and 10% phenylephrine. The mixed regimen showed greater effect of pupillary dilatation in first 15 minutes while there was no difference in final diameters in both groups. These outcomes showed that mixed regimen was as effective as conventional regimen and even greater pupil dilatation in the first 15 minutes. The mixed regimen achieved targeted 7 mm pupil diameter faster in the first 30 minutes and slightly more success at the end, although, not statistical significant (Table 3). The studies of fixed combination with varied concentration reported clinically adequate mydriatic effects.[1, 8] Likewise, the efficacy of a mixture of 0.75% tropicamide and 2.5% phenylephrine was reported faster and more successful of pupil dilatation than conventional practice.[5]

However, the mixed regimen has lower drug concentration; the pupil can be effectively

Table 4 Mean blood pressure and pulse rate between the groups and time point

		0 min	30 min	*P* - value 0 - 30	60 min	*P* - value 0 - 60
Systolic	**Conventional**	127.80 ± 13.06	129.53 ± 15.81	< 0.001*	128.17 ± 15.25	< 0.001*
	Mix	131.40 ± 14.15	129.87 ± 21.80	< 0.001*	128.03 ± 20.03	< 0.001*
	P - value	0.310	0.946		0.977	
Diastolic	**Conventional**	78.30 ± 8.60	79.47 ± 12.14	< 0.001*	78.432 ± 8.93	< 0.001*
	Mix	75.00 ± 8.16	76.53 ± 11.34	0.065	75.07 ± 10.81	0.310
	P - value	0.133	0.367		0.194	
Pulse	**Conventional**	75.83 ± 10.31	69.93 ± 9.65	0.011*	70.40 ± 9.59	0.013*
	Mix	74.73 ± 12.34	68.03 ± 9.83	< 0.001*	68.77 ± 10.86	< 0.001*
	P - value	0.709	0.464		0.446	

P - value from Mann-Whitney U-test, Independent t-test and Paired t-test

* Significant at the 0.05 level

dilated. Due to the restrict cul-de-sac reservoir, the mixed regimen does not interfere by washout effect. The onset of both mydriatic agents in mixed regimen initiated in the first application, unlike conventional regimen that have interval before instill the second mydriatic agent.[5]

In our study, the included patients were dark iris Asians. Obianwu et al studied relationship between the mydriatic action of ephredine and the color of the iris. They reported light irides more response to ephredine than dark irides.[3] Yospaiboon et al compared efficacy of phenylephrine between 2.5% and 10% concentration in dark irides and revealed superior efficacy in higher concentration of phenylephrine.[4]

The systemic side effects on arterial systolic and diastolic blood pressure showed no significant difference between groups. Our study revealed slightly increased arterial blood pressure in conventional regimen group with time. On the other hand, mixed regimen group showed slightly decreased arterial blood pressure with time. The differences of pressures in both groups compared to base lines were statistically significant but not clinically significant. Both groups showed a decreased pulse rate from the baseline. This may be explained by a reflex bradycardia due to autoregulation for preventing increase in blood pressure.[9]

A mixed regimen had lower drug concentration which minimized the risks of drug adverse effects and more tolerable. A mixture of 0.5% tropicamide and 5% phenylephrine was easy to prepare, simplified process and reduced time required to achieve desirable mydriasis. Moreover, the mixed regimen used 2 drops of mixed drug compare to 4 drops for conventional regimen, for this it may decrease the workloads in outpatient clinic setting.

Limitation in our study was unmasking mydriatic regimen due to different number of eye drop administration.

A study comparing a fixed combination of tropicamide and phenylephrine showed that lower concentration had shorter duration of action.[1] In our study, at 60 minutes, there was no patient showed regression in pupillary diameter. Further research should be investigated duration and sustainability of this mydriatic mixture to apply in a surgical setting.

In this study, the mydriatic mixture was prepared by aseptic technique for one-day use. In clinical application, sterile technique preparation of the mydriatic mixture should be concerned for safety and longer duration of storage.

The mixture of 0.5% tropicamide and 5% phenylephrine showed comparable efficacy to a conventional regimen and resulted in greater

pupillary dilatation within the first 15 minutes, allowing for more rapid achievement of desired mydriasis.

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Conflicts of interest

All authors report no conflicts of interest relevant to this article.

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