

Hemodynamic parameters of adult patients undergoing pharmacologic mydriasis using tropicamide+phenylephrine versus tropicamide alone: randomized controlled trial

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ABSTRACT

Background. Systemic absorption of topical phenylephrine administered during mydriasis may potentially cause hemodynamic changes in patients.

Objective. To compare the hemodynamic outcomes between patients given tropicamide+phenylephrine and those given tropicamide alone for mydriasis.

Design. Randomized controlled trial.

Setting. Ophthalmology Outpatient Clinic, Southern Philippines Medical Center, Davao City, from April to June 2017.

Participants. 56 male and female patients aged ≥ 19 years and scheduled for mydriasis.

Interventions. Random allocation to either one drop of 0.5% tropicamide plus 0.5% phenylephrine or one drop of 0.5% tropicamide for mydriasis of the examined eye.

Main outcome measures. Mean systolic blood pressure, mean diastolic blood pressure, mean arterial pressure, mean heart rate, and at least one episode of tachycardia or bradycardia.

Main results. Thirty (53.57%) patients received tropicamide drops, and the rest received tropicamide+phenylephrine drops. The demographic and clinical characteristics of the two intervention groups were comparable at baseline. The mean blood pressures and heart rates at 15, 30, 45, and 60 minutes postmydriasis did not significantly differ between the two groups. Four patients from the tropicamide group, and none from the phenylephrine+tropicamide group had tachycardia ($p=0.1153$). On the other hand, five patients from the tropicamide group, and four from the phenylephrine+tropicamide group had bradycardia ($p=1.0000$).

Conclusion. Hemodynamic outcomes did not significantly differ up to 60 minutes after mydriasis between patients who received tropicamide+phenylephrine drops and those who received tropicamide drops.

Keywords. blood pressure, heart rate, sympathomimetic, alpha-1-receptor agonist, antimuscarinic, parasympatholytic

INTRODUCTION

Tropicamide and phenylephrine are two of the most common agents used for pupil dilation.¹ Tropicamide is an antimuscarinic, parasympatholytic drug,^{2,4} while phenylephrine is a sympathomimetic, alpha-1-receptor agonist.⁵ Many mydriatic preparations in the market contain only either phenylephrine alone, tropicamide alone, or a combination of both. By combining both agents, a rapid and effective mydriatic effect superior to that produced by individual agents alone can be achieved.⁶ However, the absorption of these drugs during mydriasis may cause systemic adverse effects to patients.⁷

Evidences on the effect of tropicamide+phenylephrine on the hemodynamic outcomes vary in conclusion. Some studies reported that mydriasis using phenylephrine alone⁸ or the combination of tropicamide+phenylephrine⁹ has no significant effects on blood pressure and heart rate, while at least two studies^{10,11} documented that phenylephrine eye drops caused adverse

hemodynamic effects on patients.

In our setting, the kind of mydriatic agent used is dependent on the availability of the drug rather than on the risk of complications due to hemodynamic changes that can be potentially caused by the drug. On the other hand, blood pressure (BP) reading to monitor if hemodynamic changes do complicate the

IN ESSENCE

Some ophthalmic drops used for mydriasis can have systemic effects on patients.

In this randomized controlled trial of two mydriatic formulations, patients who received one drop of 0.5% phenylephrine plus 0.5% tropicamide had similar hemodynamic outcomes with those who received one drop of 0.5% tropicamide.

The added 0.5% phenylephrine on topical mydriatic agents does not affect the hemodynamic outcomes of patients up to 60 minutes postmydriasis.



mydriasis is not routinely done. We did this study to compare the hemodynamic outcomes after mydriasis between patients given tropicamide+phenylephrine and those given tropicamide alone.

METHODS

Study design and setting

We did a double-blind, randomized controlled trial with two treatment arms from April to June 2017 among patients who were scheduled to undergo mydriasis at the Ophthalmology Outpatient Clinic in Southern Philippines Medical Center, a tertiary hospital in Davao City. The clinic caters to a monthly average of 350 patients for pupil dilation.

Participants

Patients at least 19 years old with stable vital signs, who were scheduled for dilated funduscopic examination, diagnosed with cataracts, and/or screened for retinal conditions were recruited for the study.

We excluded patients who had a documented history of myocardial infarction, cerebrovascular accident, cardiac arrhythmia, hyperthyroidism, and those meeting the criteria for hypertensive urgency (>160 mmHg systolic BP) at the time of examination prior to the instillation of mydriatic eye drops. We also excluded patients who had glaucoma, active eye or lacrimal apparatus infections, lacerations of the conjunctiva/cornea, corneal abrasions, or history of hypersensitivity to mydriatic eye drops, as well as those who were pregnant or breastfeeding.

To determine the minimum sample size for the study, we assumed that the mean systolic BP of patients given tropicamide+phenylephrine drops is 137.90 ± 25.87 mmHg.⁴ Calculations were done in order for the study to detect a difference of 20 mmHg systolic BP between two groups of patients given different preparations of mydriatic eye drops. In a test for difference of two means carried out at 95% level of confidence, a total sample size of at least 54 will have 80% power of rejecting the null hypothesis if the alternative holds.

Interventions and randomization

Using simple randomization, we assigned patients to one of the two intervention groups in this study. For mydriasis of the examined eyes, patients in the first intervention group received one drop of tropicamide 0.5% plus phenylephrine 0.5%, while those in

the second intervention group received one drop of tropicamide 0.5% alone. We instructed the patients to close their eyes for at least three minutes after instillation of the mydriatic, to avoid manipulation of the eyes, and to stay calmly seated at the waiting area during the whole duration of the dilatation.

Data collection

We gathered baseline demographic and clinical data of the patients including age, sex, history of mydriasis, comorbidities, and antihypertensive medications taken, if any. We also collected the patients' systolic BP, diastolic BP, mean arterial pressure (MAP) and heart rate before mydriasis and at 15, 30, 45, and 60 minutes following the instillation of mydriatic drops, using an automated sphygmomanometer (OMRON 7 series). We told the patients to report any untoward reactions, which may warrant referral to the emergency room—headache, palpitations, tremors, dyspnea, chest discomfort, erythema, rash, eyelid edema, sweating, and dryness of mouth.

The outcome measures for this study included mean systolic BP, mean diastolic BP, mean MAP, mean heart rate, and at least one episode of tachycardia or bradycardia. We also measured mean changes in systolic BP, diastolic BP, MAP, and heart rate from baseline (before mydriasis) to 60 minutes after mydriasis.

Statistical analysis

Primary analysis for this study was done using the intention-to-treat analysis (ITT) approach. For all hemodynamic outcomes, the ITT population included all patients randomized to either of the two interventions. Missing continuous data were imputed by last-observation-carried-forward approach. To assess the robustness of the main results, we also performed per-protocol analyses that only included available data of patients who were assessed for the specific outcomes according to the protocol. Continuous data were summarized as means \pm standard deviations and compared using t-test. Categorical data were summarized using frequencies and percentages and compared using chi-square test or Fisher's exact test. A two-tailed p-value of <0.05 was considered significant. All statistical tests were done using Epi Info 7.2.2.6.

RESULTS

The primary analysis for this study included 56 patients, 26 of whom were randomized to

the tropicamide+phenylephrine group, and the remaining 30 were randomized to the tropicamide alone group. Figure 1 shows the numbers of patients involved from assessment of eligibility to end-of-study follow up. After 15 minutes of mydriasis, one patient in the tropicamide alone group had a BP of 171/98 mmHg, was admitted to the hospital emergency room for BP control, and was subsequently dropped from the study. The remaining randomized patients were assessed for the hemodynamic outcomes every 15 minutes until 60 minutes after mydriasis.

Table 1 shows the baseline characteristics of patients in both intervention groups. The two groups were comparable in terms of mean age, sex distribution, history of mydriasis, comorbidities, and maintenance medications.

Intention-to-treat analyses for the hemodynamic outcomes are shown in Table 2. The two groups were comparable in all hemodynamic outcomes at baseline, and at 15, 30, 45, and 60 minutes. The mean changes in systolic BP, diastolic BP, MAP, and heart rate from baseline (before mydriasis) to 60 minutes after mydriasis for both groups were also comparable. The rates of tachycardia and bradycardia were not significantly different between the two groups. On per-protocol analyses for data on the 30th, 45th and 60th minutes after mydriasis

(Table 2), the hemodynamic outcomes between the two groups remained comparable.

DISCUSSION

Key results

We found out in this study that, when used as mydriatics, tropicamide+phenylephrine drops and pure tropicamide drops had comparable effects on patients' blood pressures and heart rates up to 60 minutes after mydriasis.

Strengths and limitations

We were able to establish that the added 0.5% phenylephrine to tropicamide mydriatic eye drops does not increase the risk of untoward hemodynamic effects when used on patients undergoing mydriasis. However, while previous studies mentioned that the addition of phenylephrine helped increase the rapidity of mydriasis and the pupillary size during mydriasis,^{12 13} this study was not able to quantitate the time to optimal mydriasis and pupillary size during mydriasis. Quantitation of these parameters would help clinicians decide whether the change in speed and pupillary size caused by the added phenylephrine, if present, would be significant enough as to greatly affect the assessment of the internal structures of the eye.

Interpretation

Tropicamide binds to and blocks the

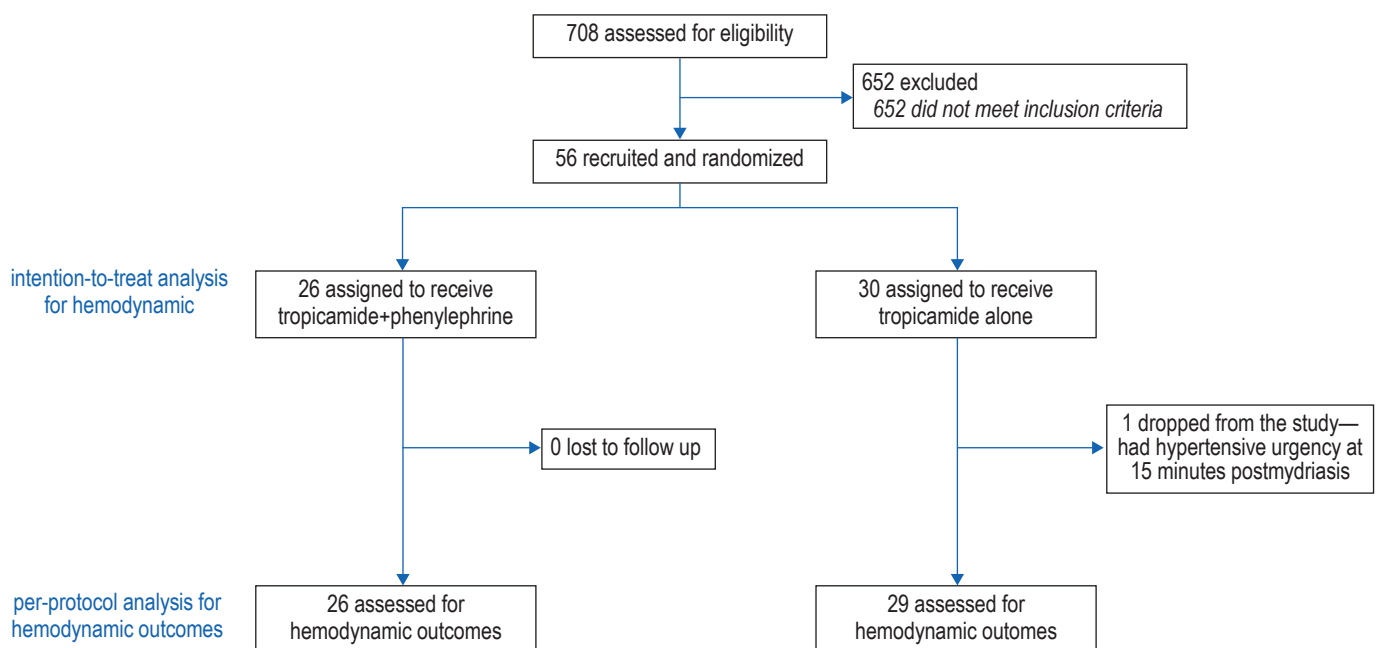


Figure 1 Screening, randomization and follow up of patients.

Table 1 Baseline characteristics

Clinical factors	Tropicamide+phenylephrine n=26	Tropicamide alone n=30	p-value
Mean age \pm SD, years	57.73 \pm 15.16	63.00 \pm 10.48	0.1321
Sex, frequency (%)			0.4890
Male	15 (57.69)	20 (66.67)	
Female	11 (42.31)	10 (33.33)	
History of mydriasis, frequency (%)*	8 (30.77)	11 (36.67)	0.6420
Comorbidities, frequency (%)			
Diabetes	6 (23.08)	11 (36.67)	0.2700
Hypertension	12 (46.15)	10 (33.33)	0.3272
Dyslipidemia	1 (3.85)	2 (6.67)	1.0000*
Benign prostatic hypertrophy	1 (3.85)	0 (0.00)	0.4643*
Bronchial asthma	1 (3.85)	0 (0.00)	0.4643*
Arthritis	0 (0.00)	1 (3.33)	1.0000*
Sleep disorder	1 (3.85)	0 (0.00)	0.4643*
Pulmonary tuberculosis	1 (3.85)	0 (0.00)	0.4643*
Maintenance medications, frequency (%)*			
ACE inhibitors	1 (3.85)	0 (0.00)	0.4643*
Beta blockers	4 (15.38)	2 (6.67)	0.4006*
Calcium channel blockers	5 (19.23)	7 (23.33)	0.7090*
Alpha 2 adrenoceptor blockers	3 (11.54)	3 (10.00)	1.0000*

* Using Fisher's exact test.

muscarinic receptors of the sphincter pupillae and ciliary muscles in the eye, producing short-acting dilatation of the pupil, and preventing the eye from accommodation for near vision.²⁻⁴ The incidence of systemic side effects for this drug is minimal due to its low affinity to muscarinic receptors and insignificant receptor occupancy in the plasma.¹⁴ However, tropicamide alone may not produce optimal mydriasis.¹²

Phenylephrine has also been used for pupil dilation. However, the use of topical phenylephrine alone as mydriatic has been reported to cause adverse cardiovascular events.⁵ In low concentrations, topical mydriatic agents produce low risks of systemic side effects, and allow faster recovery of accommodation from their cycloplegic effects.^{4,13}

Topically applied ophthalmic drugs, such as phenylephrine, are usually absorbed by the system via the following routes: conjunctiva (through conjunctival capillaries to the ophthalmic and facial veins), nasal mucosa (through the puncta of the eyelids to the nasolacrimal duct), and gastrointestinal tract (through the nasopharynx).⁷ An estimated 80% of these drugs may reach the systemic circulation and may cause adverse effects to patients.¹⁵

Our results showed comparable effects of phenylephrine+tropicamide and tropicamide alone on hemodynamic events. The dose of phenylephrine in the commercially available phenylephrine+tropicamide used for this study, i.e., 0.5%, was minimal compared to one study, which used 10% phenylephrine¹⁰ and another study which utilized 2.5% and 10% phenylephrine.¹¹ Both studies showed significant hemodynamic events when using 10% phenylephrine eye drops.^{10, 11} The amount of phenylephrine that might have gone to the patients' systemic circulation in our study was probably less than the dosage sufficient to cause significant hemodynamic events.

Generalizability

The results of this study are applicable to most patients who are scheduled for mydriasis since the demographic and clinical characteristics of our patients are similar to those of usual patients who need mydriasis as part of eye examination.

CONCLUSION

Blood pressures and heart rates of patients who were scheduled for mydriasis were comparable up to 60 minutes after mydriasis

Table 2 Intention-to-treat analysis and per-protocol analysis of outcomes

Characteristics	Intention-to-treat analysis			Intention-to-treat analysis				
	Tropicamide+phenylephrine n=26	Tropicamide alone n=30	p-value	n	Tropicamide+Phenylephrine n=26	n	Tropicamide alone n=30	p-value
SBP ± SD, mmHg								
Baseline	132.15 ± 14.20	129.87 ± 16.70	0.5863					
15 minutes	131.62 ± 14.99	130.77 ± 19.56	0.8578					
30 minutes	128.88 ± 14.96	129.33 ± 18.20	0.9209	26	128.88 ± 14.96	29	127.90 ± 16.70	0.8189
45 minutes	131.85 ± 15.75	130.30 ± 20.04	0.7522	26	131.85 ± 15.75	29	128.90 ± 18.84	0.5341
60 minutes	128.38 ± 12.98	130.67 ± 20.12	0.6223	26	128.39 ± 12.98	29	129.28 ± 18.95	0.8414
Mean change*	-3.77 ± 9.56	0.80 ± 10.48	0.0959	26	-3.77 ± 9.56	29	0.07 ± 9.86	0.1495
DBP ± SD, mmHg								
Baseline	82.35 ± 9.90	79.03 ± 10.99	0.2440					
15 minutes	82.62 ± 12.61	78.77 ± 10.05	0.2093					
30 minutes	79.92 ± 11.83	78.73 ± 10.81	0.6956	26	79.92 ± 11.83	29	78.07 ± 10.35	0.5379
45 minutes	81.19 ± 10.70	80.03 ± 10.04	0.6776	26	81.19 ± 10.70	29	79.41 ± 9.61	0.5188
60 minutes	79.88 ± 10.71	79.10 ± 11.39	0.7924	26	79.88 ± 10.71	29	78.45 ± 11.00	0.6264
Mean change*	-2.46 ± 7.15	0.07 ± 7.71	0.2109	26	-2.46 ± 7.15	29	-0.03 ± 7.82	0.2368
MAP ± SD, mmHg								
Baseline	98.95 ± 10.06	95.98 ± 11.45	0.3103					
15 minutes	98.95 ± 11.94	96.10 ± 12.29	0.3846					
30 minutes	96.24 ± 11.61	95.60 ± 12.19	0.8411	26	96.24 ± 11.61	29	94.68 ± 11.29	0.6146
45 minutes	98.08 ± 11.12	96.79 ± 12.18	0.6829	26	98.08 ± 11.12	29	95.91 ± 11.38	0.4789
60 minutes	96.05 ± 9.92	96.29 ± 13.22	0.9404	26	96.05 ± 9.92	29	95.39 ± 12.49	0.8302
Mean change*	-2.90 ± 6.49	0.31 ± 6.46	0.3808	26	-2.90 ± 6.49	29	0.00 ± 6.34	0.1002
Heart rate								
Baseline	76.08 ± 12.32	79.77 ± 14.40	0.3115					
15 minutes	73.88 ± 11.43	77.70 ± 14.60	0.2865					
30 minutes	73.19 ± 11.23	77.07 ± 12.56	0.2319	26	73.19 ± 11.23	29	77.24 ± 12.74	0.2189
45 minutes	72.58 ± 10.27	77.87 ± 13.32	0.1059	26	72.58 ± 10.27	29	78.07 ± 13.51	0.0984
60 minutes	73.27 ± 12.16	77.70 ± 13.25	0.2004	26	73.27 ± 12.16	29	77.90 ± 13.44	0.1882
Mean change*	-2.81 ± 7.69	-2.07 ± 7.26	0.7124	26	-2.81 ± 7.69	29	-2.21 ± 7.35	0.7683
Tachycardia, frequency (%)†	0 (0.00)	4 (13.33)	0.1153‡	26	0 (0.00)	29	4 (13.79)	0.1135‡
Bradycardia, frequency (%)†	4 (15.38)	5 (16.67)	1.0000‡	26	4 (15.38)	29	5 (17.24)	0.0000‡

SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial blood pressure.

* Value at 60 min - value at baseline.

† At least one episode of the outcome.

‡ Using Fisher's exact test.

between those given tropicamide+phenylephrine drops and those given pure tropicamide drops as mydriatics.

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Ethics approval

This study was reviewed and approved by the Department of Health XI Cluster Ethics Review Committee (DOH XI CERC reference P12103106).

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