Comparative mydriatic efficacy between mixture containing 0.8% tropicamide 5% phenylephrine and 0.4% and tropicamide 2.5% phenylephrine: A prospective analytical study

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Abstract

Background: This study is conducted to know the efficacy of mydriasis of diluted commercially available combination drop of tropicamide and phenylephrine. The pupillary dilation achieved with 0.8% tropicamide and 5% phenylephrine is compared with that of 0.4% tropicamide and 2.5% phenylephrine.

Methods: In this prospective analytical study conducted in 100 patients, one eye of each patient was dilated with combination drop of 0.8% and 5% phenylephrine and the other eye was dilated with a diluted concentration of the same eye drops. The drops were instilled at an interval of 10 minutes for 3 times. Mydriasis was recorded at 10, 20, 30, 40 and 60 minutes and difference between the two eyes was observed.

Results: The combination of 0.4% Tropicamide and 2.5% phenylephrine has produced an adequate mydriasis (8mm) at 30 and 40 minutes interval with a statistically significant p value of 0.045 and 0.042 respectively. The proportion of patients who required an additional application of drops after 60 minutes interval was statistically insignificant (p= 0.498). The progression of the pupil dilation at 20, 30and 40 minutes was found to be statistically significant with p values of 0.020, 0.003 and 0.022 respectively. A statistically significant difference was found in the dilation between the diabetic group and non-diabetic group at 40 and 60 minutes ($p<0.001$).

Conclusion: The diluted mixture was effective enough to produce an adequate mydriasis for intraocular examination. During the process of attaining an adequate mydriasis it also showed a significant progression in the pupillary dilation. The use of this mixture would possibly reduce the occasional adverse effects of the combination drops of higher concentrations especially in patients with co-morbid systemic conditions.

Key words: Mydriasis[1], Sympathomimetic, Parasympatholytic[3], Pupillary dilation[4], Mydriatic efficacy[2]

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Introduction

The completeness of an intraocular examination depends on adequate pupil dilation achieved by pharmacological Mydriasis[1,12]. Magnitude of dilation depends on the sphincter and dilator muscle of the pupil controlled by parasympathetic nerves and sympathetic nerves respectively[2].

Factors known to affect the pupillary response to dilation drops include pigmentation of the iris, diabetes mellitus and autonomic neuropathy, apart from any local pathology.

Phenylephrine is a sympathetic agonist that shows mydriatic effect through direct action on sympathetic nerve receptors located on the pupillary dilator muscle of the iris. It is a strong α1-receptor stimulant with little or no β receptor effect. Cardiovascular actions of phenylephrine include vasoconstriction of the systemic, pulmonary, and coronary arteries. This leads to reduction in cardiac output and renal, splanchnic, cutaneous, and limb blood flow.[3] Consequently, there is an increase in the systolic and diastolic blood pressure, tachycardia, and reflex bradycardia, side effects that are generally unwanted in the clinic.[4]

Tropicamide, on the other hand, causes mydriasis and minimal cycloplegia.[5]It is a non-selective anti-muscarinic agent devoid of vasopressor effect, giving it a clear advantage over adrenergic drug phenylephrine.

Although either class of drugs used alone can produce adequate mydriasis, studies have shown that the use of combination of a sympathomimetic drug and a para sympatholytic drug produces maximal mydriasis that is resistant to intense light stimulation.[6] Combination of both drugs also offers greater pupil dilation than single drug use.[7]

The ideal mydriatic agent should provide rapid dilation of the pupil wide enough to permit thorough ocular evaluation, without having any significant transient adverse effects.[1]

The most commonly used mydriatic agent in our outpatient department is the commercially available mixture of 0.8% Tropicamide and 5% Phenylephrine, administered 10 min apart for two to three cycles.

Repeated application of drugs was practiced to accelerate mydriasis. Since phenylephrine may be associated with dangerous cardiovascular side-effects, using lower concentrations has been suggested in vulnerable patients especially the elderly.[8]

In the backdrop of the above evidence stating the advantage of using combinations of drugs for effective mydriasis, the present study was conducted to observe whether a 50% diluted commercially available mixture was sufficient to produce equally effective mydriasis.

Methodology

This study was conducted at the outpatient unit, Department of Ophthalmology, Sri Siddhartha Medical College and Research Hospital, Karnataka.

Waiver of consent was sought and granted by the Institutional Ethics Committee as this was a part of routine ophthalmic evaluation. As per the routine protocol followed in Ophthalmology outpatient department, history was taken, visual acuity was recorded, diffuse light examination and slit lamp examination was done. Baseline pupillary size was recorded using transparent scale or Schirmer's strips by the same examiner at ambient light.

The commercially available mixture of 0.8% tropicamide and 5% phenylephrine was diluted with 1:1 concentration of commercially available carboxymethyl cellulose to achieve a concentration of 0.4% tropicamide and 2.5% phenylephrine. The commercially available eye drop was instilled in the right eye and the diluted mixture was instilled in the left eye. To avoid bias, the mixture was prepared in the commercially available dropper bottle only and 2 separate bottles were labelled R (commercially available drop) & L (diluted drop) and were instilled by Interns. The study was double blinded for this stage. The drops were repeated after 10 minutes in both eyes 3 times or until the end point was reached i.e. 8 mm of pupil size. (If reached within the time frame of 30 minutes).

Application of drops was stopped once the pupil diameter reached 8mm and sustained dilation with LED torch.

All patients requiring dilation of pupil, attending outpatient department of Sri Siddhartha medical college, from august 2015 to December 2015 were included in the study.

Exclusion criteria included less than 18 years of age, past history of ocular injuries /surgeries, LASER treatment, history of current use of any miotic drugs, hypertension/cardiac disease. Presence of pupillary abnormalities, ocular infection/inflammation, and shallow anterior chamber also formed exclusion criteria. Patients who required Intra ocular pressure measurement were excluded from the study.

All the participants were explained about the study, their assent was taken and routine protocol of history, visual acuity and diffuse light examination were done. A preliminary slit lamp examination was done to rule out exclusion criteria.

A total number of 100 consecutive patients, attending the OPD for routine ophthalmic examination were observed. The patients were informed about the instillation of drops, the possibility of transient stinging and the blurring to be expected following mydriasis. As per the protocol, separate drops were instilled in the right (control) and left (study) eyes by Interns, one after the other. One drop was instilled in the lower fornix by pulling the lower lid and the patients were instructed to keep the lids gently closed. Drops were instilled at 0, 10, 20 & 30 minutes, right eye followed by the left eye, after the recording of pupillary diameter. Pupil size was measured by the 2nd author every 10 minutes up to 40 minutes in both eyes, and recorded separately. A total of 4 test readings were taken. In patients who failed to achieve study end point at 40th minute, 1 more reading was taken at 60th minute. Difference of mydriasis between the control & the study eyes, if any was also noted.

During the course of the study, it was observed that poor pupil dilatation was common in diabetic patients. The patients were therefore classified as diabetics and non-diabetics by their clinical profile.

Results

A total of 100 patients participated in the study. Forty eight were females (48%) and fifty two were males (52%). Forty three were diabetic and fifty seven were non-diabetic. Age group of the patients ranged from 20 to 70 with mean±SD of 41.73±17.3. Characteristics of the study subjects are shown in Table 1.

Table 1: Characteristics of Study subjects

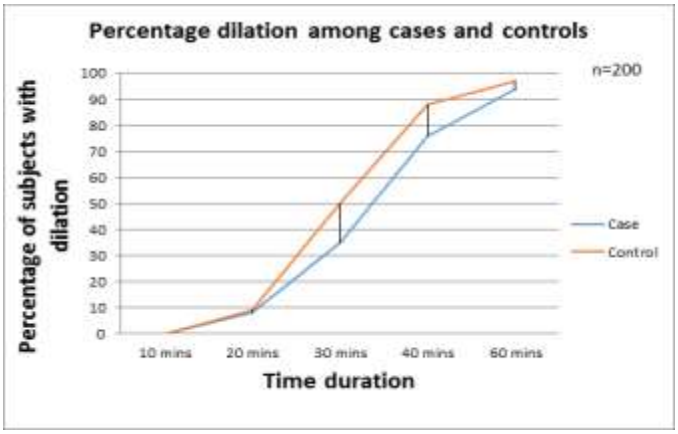
Characteristic	**Mean ± SD**	
Age	41.73±17.3	
	Number	**%**
Gender		
Male	52	52.0
Female	48	48.0
Diabetic status		
Diabetic	43	43.0
Non-diabetic	57	57.0

9 patients in the control group and 8 patients in the study group could attain study end point dilation of 8mm after 20 minutes (P=1.00) whereas 50 patients in control group and 35 patients in the study group attained full dilation after 30 minutes (p=0.045). With 3 applications almost 88% in the control group and 76% in the study group were dilated. All the patients were observed till 60 minutes. The proportion of patients who required an additional application of drops after 60 minute interval of time was three in control group and 6 in study group (p = 0.498). The summarized analysis is shown in Table 2.

Table: 2 Time difference between case and control for dilatation n - 200

Time of onset of dilatation	Study group N (%)	Control group N (%)	P value
After 10 mins			
Dilated	0(0)	0(0)	--
Non-dilated*	100 (100)	100 (100)	
After 20 mins			
Dilated	8 (8.0)	9 (9.0)	1.000
Non-dilated	92 (92.0)	91 (91.0)	
After 30 mins			
Dilated	35 (35.0)	50 (50.0)	0.045
Non-dilated	65 (65.0)	50 (50.0)	
After 40 mins			
Dilated	76 (76.0)	88 (88.0)	0.042
Non-dilated	24 (24.0)	12 (12.0)	
After 60 mins			
Dilated	94 (94.0)	97 (97.0)	0.498
Non-dilated	06 (6.0)	03 (3.0)	

*Baseline pupil



The progression of the pupil dilation is shown in the Table 3. The ***p*** value at 20, 30, 40 and 60 minutes are 0.020, 0.003, 0.022 and 0.189 respectively ($p<0.5$, is statistically significant). The pupil dilatation was observed till 60 minutes and the mean±SD was not found statistically significant at 60 minutes.

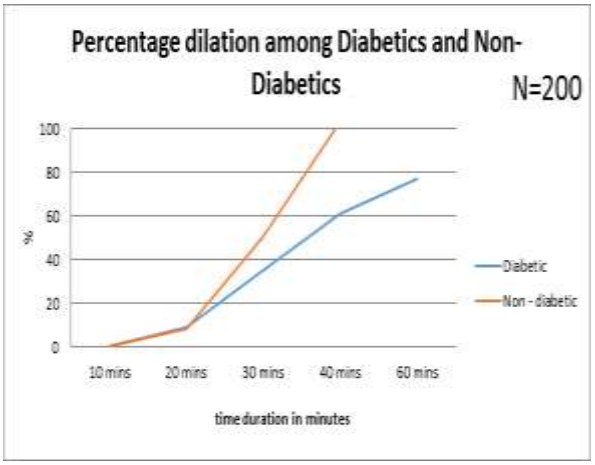
Table 3: Progression of the pupil dilation

Time	Type of subject	Mean±SD	P value
After 10 minutes	Study	4.38±0.89	0.081
	Control	4.60±0.89	
After 20 minutes	Study	5.50±1.21	0.020
	Control	5.89±1.14	
After 30 minutes	Study	6.77±1.15	0.003
	Control	7.21±0.92	
After 40 minutes	Study	7.66±0.70	0.022
	Control	7.85±0.44	
After 60 minutes	Study	7.92±0.34	0.189
	Control	7.97±0.17	

A statistically significant difference was found in the dilation between the diabetic group and non-diabetic group at 40 and 60 minutes ($p<0.001$) as shown in the following Table 4.

Table 4: Dilation on the basis of clinical profile of Diabetic or Non diabetic status. n -200

Time of onset of dilation	Diabetic N (%)	Non – diabetic N (%)	P value
After 10 minutes			
Dilated	0(0)	0(0)	--
Non-dilated	86 (100)	114 (100)	
After 20 minutes			
Dilated	9 (10.5)	08 (7.0)	0.447
Non-dilated	77 (89.5)	106 (93.0)	
After 30 minutes			
Dilated	35 (40.7)	50 (43.9)	0.668
Non-dilated	51 (59.3)	64 (56.1)	
After 40 minutes			
Dilated	61 (70.9)	103 (90.4)	< 0.001
Non-dilated	25 (29.1)	11 (9.6)	
After 60 minutes			
Dilated	77 (89.5)	114 (100.0)	< 0.001
Non-dilated	09 (10.5)	0 (0)	



Observation

A thorough intraocular examination depends on adequate mydriasis. The ideal mydriatic eye drop should provide adequate dilatation without having any adverse effects.[1,12]

Combination drugs are more commonly used in ophthalmic practice to achieve adequate pupil dilation. The effect of tropicamide to dilate the pupil or achieve mydriasis is by relaxation of the iris sphincter muscle whereas phenylephrine is by stimulation of the dilator muscle. Tropicamide is a muscarinic receptor blocker. It non-selectively inhibits the muscarinic actions of Acetylcholine. It blocks the cholinergic nerves supplying the smooth muscles of iris and produces mydriasis and causes paralysis of ciliary muscle preventing eye from accommodating for near objects and also produces a tightening of the suspensory ligament and results in flattening of the lens and a consequent increase in focal length. While phenylephrine binds to post synaptic alpha1 adrenergic receptors that are present on the sympathetic nerves that supply the dilator muscle. The use of mixture of tropicamide and phenylephrine is effective and usually safe. In rare cases systemic side effects like tachycardia and elevated blood pressure can occur as most of the drug is available for systemic absorption via nasolacrimal duct. To avoid these systemic complications diluted concentrations of the commercially available drops was prepared using 1:1 carboxymethyl cellulose and the efficacy was observed. Also, the diluted mixture can be used in paediatric age group, if found equally efficacious. In a study conducted by *Orhan Elibol et al.* about the systemic side effects of mydriatics it was found that lower concentrations of mydriatics can prevent the possible systemic side effects in children.[9]

Baseline pupillary size was recorded in millimetres using transparent scale. Every 10 minutes the measurement was repeated, until 8mm dilation was achieved. In those who did not reach 8mm dilation, if the pupillary size remained status quo on 2 consecutive readings, it was taken as the end point. Also, the dilation at 60 minutes was recorded in all the 200 eyes.

In this observational study comparing the efficacy, it was found that despite lower concentrations, the pupillary dilatation was rapid and almost similar to the effect of the commercially available concentration we routinely use. *Apt et al.* studied a combination of 0.5% tropicamide and 2.5% phenylephrine in patients aged between 16 to 84 years.[10] This mixture produced pupil dilatation to 7 mm within 60 min. Its potency was equal to a combination of 0.8% tropicamide and 5% phenylephrine. They also found that pupils of younger patients dilated better than those of the older. *Krumholz et al.* showed equivalent effects of solutions containing 0.5% tropicamide with either 2.5% or 1.25% phenylephrine. All pupils reached at least 7 mm in diameter within 30 min.[11]

Our study consisted of older people (average age 41.73±17.3 years) and diabetics. Among the diabetics,

we observed that patients with poor dilation had higher glucose levels on the day of dilation. Probably, metabolic control of diabetes may influence pupillary dilation/ effect of the topical drops. This needs to be confirmed by a systematic randomized control trail.

Limitations of our study is the way of measurement of the pupillary diameter as it is the subjective measurement of the pupil size performed external to the cornea. However, the method used was sufficient for detecting meaningful data for the study.

Conclusion

In conclusion, the diluted mixture of 0.4% Tropicamide and 2.5% Phenylephrine was effective enough to produce adequate pupillary dilatation for intraocular examination. The use of this mixture would possibly reduce the occasional adverse effects of the combination drops of higher concentrations especially in patients with co-morbid systemic conditions.

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