

A Study to Investigate the Clinical Potentiating Effect of Topical 0.5% Proparacaine on 0.8% Tropicamide-5% Phenylephrine-Induced Mydriasis**D. Satyavardhan Rao¹, G. Sireesha², Praveen Kumar K. V.³, K. Manaswini⁴, B. Kavitha⁵**¹Associate Professor, Department of Ophthalmology, Govt. A.C.S.R Medical College, Nellore, [A.P], India²Assistant Professor, Department of Ophthalmology, Govt. A.C.S.R Medical College, Nellore, [A.P], India³Assistant Professor, Department of Ophthalmology, Govt. A.C.S.R Medical College, Nellore, [A.P], India⁴Senior Resident, Department of Ophthalmology, Govt. A.C.S.R Medical College, Nellore, [A.P], India⁵Post Graduate Department of Ophthalmology, Govt. A.C.S.R Medical College, Nellore, [A.P], India

Received: 24-07-2024 Revised: 24-08-2024 / Accepted: 24-08-2024

Corresponding author: Dr. Gundeboyana Sireesha

Conflict of interest: Nil

Abstract**Background:****Aim:** To Study whether prior instillation of 0.5% Topical proparacaine potentiates mydriasis by 0.8% Tropicamide- 5% phenylephrine-induced mydriasis**Objectives:** 1) To compare the mydriatic efficacy of a 0.8% Tropicamide and 5% Phenylephrine combination with or without prior instillation of 0.5% Topical Proparacaine in patients attending the Outpatient Department of Ophthalmology, ACSR Government General Hospital, Nellore. 2) To Study the rate and magnitude of pupillary dilation.**Methodology:** In this study, 60 patients and a total of 120 eyes were examined as a part of a routine eye evaluation. The right eye was considered the study eye, and the left eye was considered the control eye. The study eye was given proparacaine 0.5% eye drops before receiving commercially available tropicamide 0.8% - phenylephrine 5% eye drops, while the control eye received only the combination drops. The size of the pupils was measured and recorded at baseline, 10, 20, and 40 minutes after instilling the mydriatic agent. The endpoint was considered to be a dilation of 8mm or at the end of 40 minutes.**Results:** In both the study group and the control group, the baseline (0 minutes) pupil diameter was 2.5±0.5 mm. After 20 minutes, the mean pupillary diameter in the study group was 5.5±0.5 mm, while in the control group, it was 5 ± 0.5 mm. At 40 minutes, the pupillary diameter was 8±0.5 mm in the study group and 7.5 ± 0.5 mm in the control group.**Conclusion:** Therefore, we recommend using Topical proparacaine 0.5% before applying Topical 0.8% Tropicamide-5% Phenylephrine to achieve faster dilation of the pupil.**Keywords:** Proparacaine 0.5%, Phenylephrine 5%, Tropicamide 0.8%.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Pupil dilation is a crucial part of routine eye examinations, particularly for evaluating the posterior segment of the eye. It is also essential for various intraocular surgeries such as cataract and vitreoretinal surgeries and outpatient laser procedures [4].

Tropicamide is a cholinergic antagonist and a non-selective muscarinic blocker that adheres to almost all muscarinic receptor subtypes. It relaxes the iris sphincter, leading to mydriasis (pupil dilation) with minimal cycloplegic action [1]. Phenylephrine, on the other hand, is a sympathomimetic drug. When instilled in the eye, it causes vasoconstriction of conjunctival vessels. It acts as a mydriatic as it

constricts the dilator muscle of the iris. It is an alpha-adrenergic agonist regularly used for dilation of pupils. It is also used in intraocular surgeries as a component of pre-operative regimens. Proparacaine hydrochloride is a fast-acting local anaesthetic used before assessing intraocular pressure, corneal foreign bodies removal, corneal scrapings, and Gonioscopic evaluation. It is also used as a topical anaesthetic before cataract surgery.

In addition to its anaesthetic action, it has been suggested that proparacaine instillation before the mydriatic application can hasten pupillary dilation and increase the extent of pupillary dilation. It alters and disrupts the corneal epithelium and helps

in more absorption of the mydriatic agent into corneal layers [1,2,3].

Material and Methods

Study Protocol: It is a prospective-comparative study conducted at the Ophthalmology Department, ACSR Government General Hospital, Nellore.

Study Duration: 3 months

Sample Size: The study included 60 patients for 120 eyes after they met the inclusion and exclusion criteria.

The following prospective comparative study was conducted in the Ophthalmology Department at ACSR Government General Hospital in Nellore from April 2024 to June 2024. The study involved 120 eyes of 60 patients who required dilatation of the pupil as a part of their eye examination. Patients were informed about the potential blurring effect of the mydriatic, and consent was obtained for the study. Consent from the parents was obtained for patients <18 years old.

Inclusion Criteria:

1. 15-60 years age group patients visiting the Outpatient Ophthalmology Department, ACSR Government General Hospital were included in this study.
2. Patients who have provided informed consent for the study.

Exclusion Criteria:

1. One-eyed patients were excluded from this study.
2. Patients with pupillary abnormalities, Pseudo-exfoliation.
3. Patients with previous intraocular inflammation like uveitis.
4. Patients with Diabetes mellitus, Hypertension, and Benign prostatic hyperplasia [5].
5. Patients with corneal opacities.
6. Patients who underwent intraocular surgeries.
7. Patients with a previous known history of allergy to Tropicamide [8] -phenylephrine [9], and proparacaine eye drops [10].

Methodology

The participants underwent a routine eye examination, including history taking, assessing visual acuity, slit lamp biomicroscopic examination, and fundus evaluation. The patients were informed about the need for mydriasis, as well as the associated side effects such as tearing and temporary stinging.

The patients were made to sit comfortably with their heads resting, ensuring optimal comfort and relaxation during the procedure. The patients were asked to look far and the initial pupillary diameter was recorded in both eyes. We used a transparent

scale for measuring the vertical diameter in millimetres of both pupils in ambient light. The scale was placed on the margin of the supraorbital rim and held in the mid-pupillary line. For every patient, pupillary diameter was measured by the same examiner. The right eye was designated as the study eye, while the left eye served as the control eye. [7]. The right eye will be given Proparacaine 0.5% first and then after a 2-minute interval, mydriatic eye drops (Tropicamide 0.8% and Phenylephrine 5%) were applied in the right eye. simultaneously the left was also given mydriatic eye drops. We repeated the same process at 10,20, and 40 minutes after the application of the initial drop. To maximize the contact period of the drug with the eye punctal occlusion was done for at least 1 minute after each drop instillation [7]. The size of the pupil was measured four times in total -at baseline (0 minutes), and at 10,20, and 40 minutes. The trial concluded when the pupil reached a size of 8mm, or at the end of 40 minutes. Pupillary diameter was measured (a) To compare the time taken for the onset of mydriasis, and (b) To compare the time interval to achieve the maximum amount of mydriasis.

Observation and Results:

This data was compiled using Microsoft Excel. The data analysis was done with IBM SPSS version 29.0. An unpaired Student's t-test was calculated using a Graph Pad t-test calculator to determine the differentiation between both groups. P-value <0.05 was considered significant statistically for all practical purposes. 120 eyes of 60 consecutive patients were taken into the study, with 28 male and 32 female participants (refer to Table 1). The patient's ages ranged from 15 to 60 years. A difference in pupillary diameter which was statistically significant was observed in both the study and control groups at the end of 10 minutes ($p < 0.0001$), at the end of 20 minutes ($p < 0.0001$), and at the end of 40 minutes ($P < 0.0001$) (refer to Table 2 and Figure 3). By the end of 40 minutes, the study group attained a pupillary dilation of 8.00 mm, and the control group attained 7.50mm.

In this study, most of the 60 study eyes (93.34%) showed a dilation of 8.0 ± 0.50 mm, which was statistically significant. Only a small percentage (6.66%) did not experience this level of dilation. In comparison, 37 out of the 60 control eyes (61.66%) did not show a dilation of 8.0 ± 0.50 mm. Still, it developed a dilatation of 7.0 ± 0.5 mm, while 23 out of the 60 control eyes (38.33%) developed a dilatation of 7.5 ± 0.5 mm. In the study group in which proparacaine and mydriatic eye drops were given, the pupillary diameter increased from 2.5 ± 0.5 mm at 0 minutes to 8.0 ± 0.5 mm at the end of 40 minutes in 93.34% of study eyes. In the control group which received only mydriatic eye drops the dilation of the pupil increased from 2.5 ± 0.5 mm at

0 minutes to 7.5 ± 0.5 mm at the end of 40 minutes
in 38.33% of control eyes and to 7.0 ± 0.5 mm in

61.66% control eyes.

Table 1: Population Distribution as per Age and Sex of the individuals.

Age (years)	Gender (Males)	Gender (Females)
15-25	04	09
26-35	07	14
36-45	10	05
46-55	05	03
56-60	02	01
Total	28	32

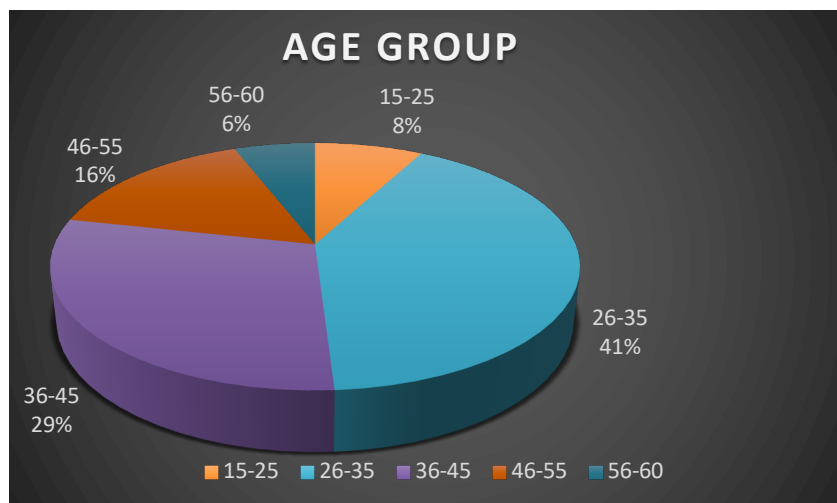


Figure 1: Distribution of Frequency as per patient's age group

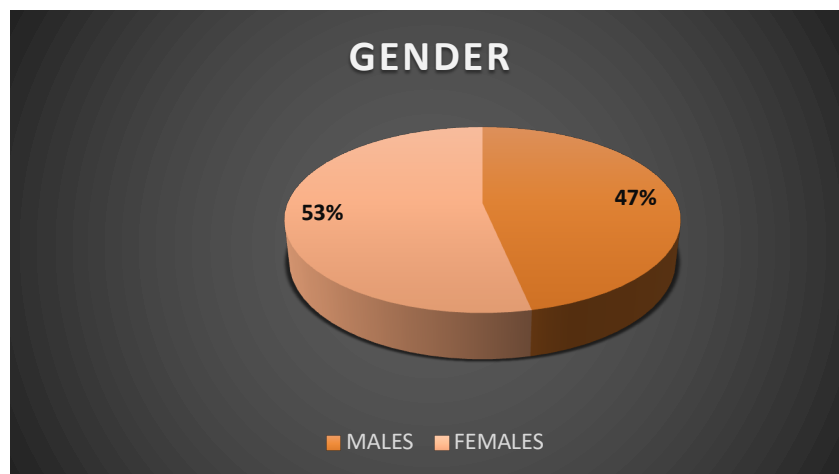


Figure 2: Distribution of Frequency as per patient's gender

Table 2: Effect of proparacaine on mydriatic eye drops in the study group (RE) and only mydriatic eye drops in the control group (LE) at corresponding time intervals -comparative study.

Mydriatic effect at different time intervals	Pupil size (mm) (Study group)-OD/RE Proparacaine 0.5%+ Tropicamide 0.8% and Phenylephrine 5%(mean±SD)	Pupil size (mm) (Control group)-OS/LE Tropicamide 0.8% and Phenylephrine 5%(mean±SD)	p-value
0 min	2.5 ± 0.5 mm	2.5 ± 0.5 mm	not significant
10 min	3.5 ± 0.5 mm	3.0 ± 0.5 mm	<0.0001
20 min	5.5 ± 0.5 mm	5.0 ± 0.5 mm	<0.0001
40 min	8.0 ± 0.5 mm	7.5 ± 0.5 mm	<0.0001

SD: Standard Deviation

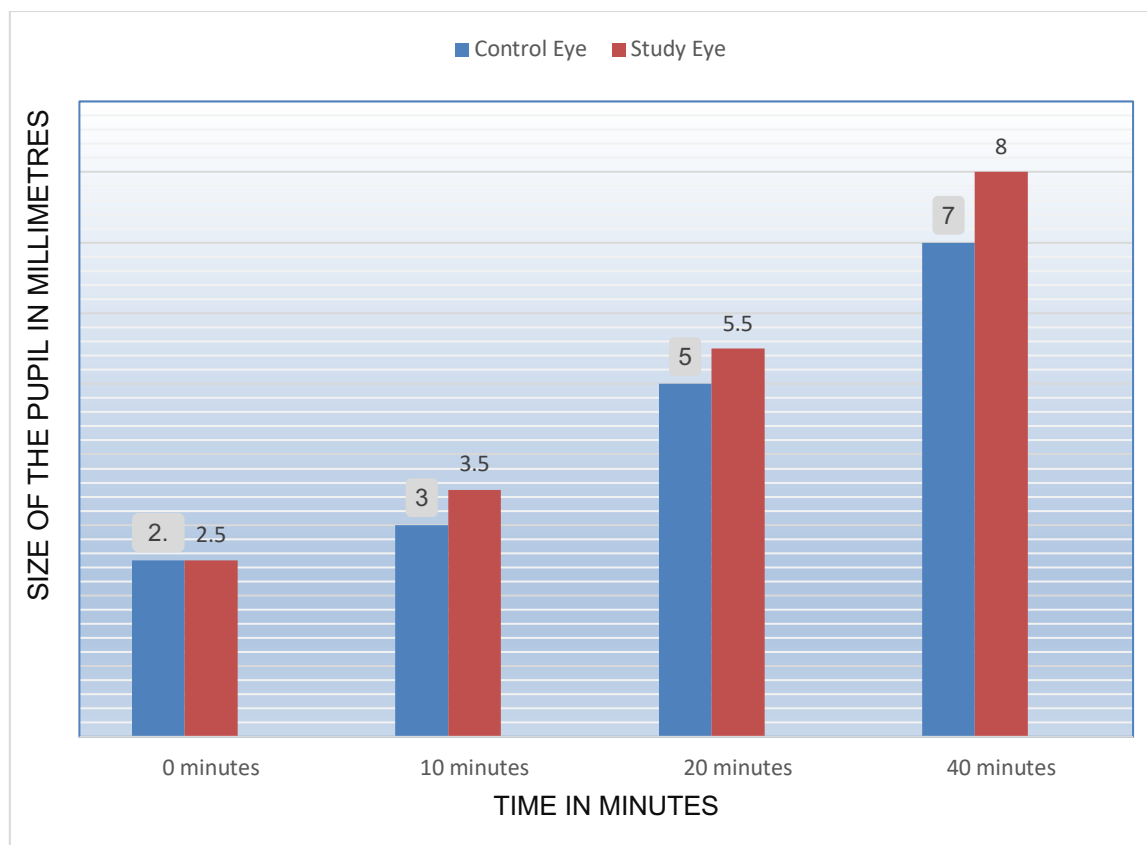


Figure 3: Effect of proparacaine on mydriatic eye drops in the study group (RE) and only mydriatic eye drops in the control group (LE) at corresponding time intervals -comparative study

Table 3: Diameter of Pupils in the study group (RE) and in the control group (LE).

Time in minutes (RE, LE)	Pupil diameter (mm)	Standard Deviation	Standard Error of Difference	SEM	t value	p-value	Association between two groups
RE 0 min	2.50	0.50	0.0091	0.065	0.0000	1.0000	Not statistically significant
LE 0 min	2.50	0.50	0.0091	0.065			
RE 10 min	3.50	0.50	0.0091	0.065	5.4772	<0.0001	Statistically significant
LE 10min	3.00	0.50	0.0091	0.065			
RE 20min	5.50	0.50	0.0091	0.065	5.4772	<0.0001	Statistically significant
LE 20min	5.00	0.50	0.0091	0.065			
RE 40 min	8.00	0.50	0.0091	0.065	5.4772	<0.0001	Statistically significant
LE 40min	7.50	0.50	0.0091	0.065			

Table 4: This table presents the gender-based distribution of individuals in percentages in our study compared to Menishinkai JP et al [3].

Gender	Our study	Menishinkai JP et al
Males	28 (47%)	22 (38.6%)
Females	32 (53%)	35 (61.4%)

Table 5: This table presents the gender-based distribution of individuals in percentages in our study compared to Sandhya et al [1].

Gender	Our study	Sandhya et al [1]
Males	28 (47%)	52 (52%)
Females	32 (53%)	48 (48%)

Table 6: This table presents the mydriatic effect at different intervals compared to our study and the study by Sandhya et al [1].

Mydriatic effect at different time intervals	Our study		Sandhya et al [1]	
	Study group (mm)	control group (mm)	Study group (mm)	control group (mm)
0 min	2.50±0.50	2.5±0.50	2.61±0.49	2.61±0.49
10 min	3.50±0.50	3.0±0.50	4.23±0.73	3.67±0.88
20 min	5.50±0.50	5.0±0.50	6.19±0.61	5.52±0.89
40 min	8.00±0.50	7.5±0.50	7.75±0.45	7.28±0.76

Discussion

The pupil is the opening in the iris diaphragm, slightly to the nasal side. It is controlled by the intrinsic muscles present in the iris, namely the sphincter pupillae and the dilator pupillae. The oculomotor nerve carries parasympathetic fibers to the ciliary ganglion, where the postganglionic fibers innervate the sphincter pupillae, causing the pupil to constrict. Conversely, pupil dilation is mediated by the dilator pupillae, which is supplied by cervical sympathetic fibers. Adrenaline, phenylephrine, hydroxy amphetamine, cocaine, and ephedrine are classified as sympathomimetic mydriatics, while atropine, homatropine, cyclopentolate, and tropicamide are classified as parasympatholytic mydriatics. Adequate mydriasis is crucial for a comprehensive intraocular examination, and it can be effectively achieved using a suitable topical mydriatic with minimal side effects. In modern practice, a combination of tropicamide-phenylephrine eye drops is utilized to attain pupillary dilatation. Tropicamide inhibits the muscarinic action of acetylcholine and relaxes the sphincter pupillae effectively. It results in mydriasis and ciliary muscle paralysis, ultimately leading to accommodation loss. Phenylephrine is a sympathomimetic drug; it causes constriction of dilator pupillae muscle leading to mydriasis of the pupil.

The study excluded patients with Diabetes mellitus because autonomic neuropathy can lead to reduced pupil motility and corneal sensitivity [11]. Patients who were being treated with Tamsulosin for Benign Prostatic Hyperplasia were excluded due to the intraoperative complication of floppy iris syndrome. Tamsulosin is an α -1 antagonist used to treat urinary retention, but it can cause dilator muscle disuse atrophy. It works by blocking α -1 adrenergic receptors in the iris muscles, which weakens mydriasis [5].

In pseudo-exfoliation, grey-white flaky material is deposited on the pupillary border of the iris, trabecular meshwork, and the anterior chamber angle. So, the patients having pseudo-exfoliation have been excluded from the study due to poor mydriasis [12]. A topical anaesthetic before administering mydriatic into the eyes is applied routinely in day-to-day clinical practice [6]. Local

anaesthetics can induce subclinical micro-epithelial changes in the cornea. These changes will cause more contact time of the drug with the eye, therefore decreasing the time taken for maximum pupillary dilation, increasing the maximum dilatation of the pupil, and prolonging the effect of mydriatic by enhancing the trans-corneal permeability of the drug.

Our study focused on the potential of proparacaine to enhance the effectiveness of tropicamide and phenylephrine eye drops in dilating pupils. We used a transparent scale to measure the initial pupil size in milli-metres and monitored the endpoint. The target pupil size was either 8 mm or achieved within 40 minutes. Our study revealed that the study group, which used proparacaine in addition to mydriatic drops, experienced faster pupil dilation compared to the control group, which only used mydriatic drops (p-value of <0.0001).

Conclusion

In modern ophthalmic practice, particularly in busy urban areas where patients prefer shorter wait times for eye examinations, we recommend topical proparacaine 5% before administering a mydriatic agent. This method results in quicker pupil dilation, reduces waiting periods, and helps alleviate the temporary stinging and discomfort often associated with common mydriatic agents.

Reference

1. Sandhya R, Ponnat AK. Effectiveness of Topical Proparacaine 0.5% to Augment the Mydriatic Effect of Tropicamide: Phenylephrine Combination Eye Drops. *Int J Sci Stud*. 2016; 4(7):100-104.
2. Chellakumar, V., and D. Ravindran. "A Study Of The Potentiating Effect Of Topical Proparacaine 0.5% On Tropicamide 0.8% And Phenylephrene 5% Induced Mydriasis In A Southindian Population". *Asian Journal of Pharmaceutical and Clinical Research*, vol. 14, no. 6, June 2021; 60-61, doi:10.22159/ajpcr.2021.v14i6.41587.
3. Menishinkai, J. P., Pujar, C., Manasa, C. N., Dasar, L. V., & Salagar, M. C. A quasi-experimental study to assess the effect of a local anaesthetic proparacaine on tropica mide-induced pupillary dilation. *International*

- Journal of Basic & Clinical Pharmacology, 2017; 4(3): 410–413. <https://doi.org/10.18203/2319-2003.ijbcp20150046>.
4. Singh, Punit Kumar, and Ananya Singh. Effect of Topical Proparacaine 0.5% on Tropicamide-Induced Mydriasis. *Ophthalmology Research: An International Journal*. 2020; 12(2):1-5. <https://doi.org/10.9734/or/2020/v12i230141>.
 5. Shtein RM, Hussain MT, Cooney TM, Elner VM, Hood CT. Effect of tamsulosin on iris vasculature and morphology. *J Cataract Refract Surg*. 2014 May; 40(5):793-8. doi: 10.1016/j.jcrs.2013.10.031. Epub 2014 Mar 14. PMID: 24631201; PMCID: PMC4392814.
 6. Haddad DE, Rosenfield M, Portello JK, Krumholz DM. Does prior instillation of a topical anaesthetic alter the pupillary mydriasis produced by tropicamide (0.5%)? *Ophthalmic Physiol Opt*. 2007 May; 27(3):311-4. doi: 10.1111/j.1475-1313.2007.00472.x. PMID: 17470245.
 7. Ogun OA, Oliver JW, Ashaye AO, Ajayi BG. Evaluating the potentiating effect of amethocaine on tropicamide-induced mydriasis in darkly pigmented irides, using infrared pupillometry. *Ophthalmol Eye Dis*. 2014 Apr 8; 6:13-9. doi: 10.4137/OED.S13991. PMID: 24812528; PMCID: PMC4001628.
 8. Yelne S, Pendam M (April 10, 2024) Allergic Reaction to Tropicamide Eye Drops: A Case Report. *Cureus* 16(4): e57945. doi: 10.7759/cureus.57945.
 9. Vu B, Wong A, Marcus-Freeman S. Allergic Reaction to Phenylephrine. *Fed Pract*. 2017 Feb; 34(2):41-44. PMID: 30766257; PMCID: PMC6372024.
 10. Dannaker CJ, Maibach HI, Austin E. Allergic contact dermatitis to proparacaine with subsequent cross-sensitization to tetracaine from ophthalmic preparations. *Am J Contact Dermat*. 2001 Sep; 12(3):177-9. doi: 10.1053/ajcd.2001.23006. PMID: 11526525.
 11. Clausen S, Jørgensen CM and Bek T. The Effect of Topical Anesthesia on Pharmacological Mydriasis in Diabetic Patients Depends on the Presence of Retinopathy. *Austin J Clin Ophthalmol*. 2015; 2(4): 1056.
 12. N.I. Watson, S. Winder and F. D. Green. *Aberdeen Eye*. 1995;9: 341-343.