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Original Research Article

A Comparative Study on the Efficacy and Side Effects of Eye Drop Tropicamide versus Combination of Eye Drop Tropicamide and Phenylephrine for Mydriasis and Cycloplegia

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Abstract

Background: The use of mydriatic and cycloplegic eye drops is a common practice in ophthalmology for various diagnostic and therapeutic procedures like for estimation of refractive error and for thorough fundus examination. The combination of Tropicamide and Phenylephrine has been a subject of debate among ophthalmologists regarding its efficacy and side effects.

Aims and Objectives: The aim of this study was to evaluate the efficacy and safety of 1% Tropicamide alone versus a combination of 0.8% Tropicamide and 5% Phenylephrine for mydriasis and cycloplegia. The objectives were to compare the rate of mydriasis and maximal mydriasis after instilling a single drop of each solution and to measure the degree of cycloplegia and amount of residual accommodation at 25 minutes after instillation of the drops.

Methods: This was a hospital-based, analytic cross-sectional study conducted on 100 patients between 15 and 35 years of age presenting to the Department of Ophthalmology, Government Medical College and Associated Group of Hospitals, Kota for refraction or fundus examination. Patients were randomly assigned to either the Tropicamide group or the Tropicamide-Phenylephrine group. The study measured the rate of mydriasis, maximal mydriasis after eye drop instillation. Study also measured the degree of cycloplegia and amount of residual accommodation at 25 minutes after instillation of the drop.

Results: The combination of Tropicamide and Phenylephrine resulted in a higher rate of mydriasis and maximal mydriasis than Tropicamide alone. Tropicamide alone uncovered significantly higher mean latent error of refraction and had higher cycloplegic effect as compared to combination group. The study also found that increasing age lead to increased cycloplegia and decreased residual accommodation in both groups. It was also found that both groups had a similar safety profile, with no significant adverse effects observed except significant increase in pulse rate after instillation of combination eye drop.

Conclusion: The combination of Tropicamide and Phenylephrine is more effective than Tropicamide alone for inducing mydriasis with a similar safety profile except significant change in pulse rate. While Tropicamide alone had better cycloplegic effect.

Keywords: Tropicamide, Phenylephrine, Mydriasis, Cycloplegia, Efficacy, Safety.

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Introduction

The use of mydriatic and cycloplegic eye drops is a common practice in ophthalmology for a variety of diagnostic and therapeutic procedures. Precise estimation of refractive errors and a thorough fundus examination commonly requires these eye drops.

Among the drugs used for this purpose, Tropicamide is a widely used anticholinergic/parasympatholytic agent that causes mydriasis and cycloplegia. However, its effect may not be sufficient for some clinical scenarios, and additional medication may be required. Phenylephrine, a sympathomimetic drug, is often used in combination with Tropicamide to achieve a more profound mydriatic effect.

The combination of Tropicamide and Phenylephrine has been a subject of debate among ophthalmologists regarding its efficacy and side effects. Some studies have suggested that the combination provides better mydriatic and cycloplegic effects with minimal side effects, while others have reported adverse effects such as increased intraocular pressure, discomfort, and blurred vision.

For instance, a study by Chowdhury *et al* found that the combination of Tropicamide and Phenylephrine provided better mydriatic and cycloplegic effects compared to Tropicamide alone. The study also reported minimal adverse effects with the combination treatment [1].

Another study by Gills *et al* found that the combination of Tropicamide and Phenylephrine provided a more complete and predictable dilation of the pupil, which was useful for surgical procedures. The study reported that the combination treatment was well-tolerated and had minimal side effects [2].

However, a study by Hutchings *et al* reported that the use of Tropicamide and Phenylephrine for mydriasis can lead to an increase in intraocular pressure in some patients, which could potentially result in glaucoma. The study recommended caution in the use of these drugs in patients with known glaucoma or other risk factors for elevated intraocular pressure [3].

These findings highlight the potential benefits and risks associated with the combination of Tropicamide and Phenylephrine, and underscore the need for further research to fully evaluate its efficacy and safety. The proposed study aims to provide additional information on this topic, which can help to inform clinical practice and improve patient outcomes.

So, this comparative study was aimed to evaluate the efficacy and safety of 1% Tropicamide alone versus a combination of 0.8% Tropicamide and 5% Phenylephrine for mydriasis and cycloplegia. The outcome measures will include the rate of mydriasis and maximal mydriasis after instilling single drop of each solution and to measure the degree of cycloplegia and amount of residual accommodation at 25 minutes after instillation of drop.

The findings of this study will help to inform the choice of medication for mydriasis and cycloplegia in clinical practice, taking into account both efficacy and potential side effects.

Methods

This hospital based analytic cross-sectional study was conducted on 100 patients between 15 and 35 years of age presenting to the Department of Ophthalmology, Government Medical College and Associated Group of Hospitals, for refraction or fundus examination between December 2020 to December 2021 after ethical approval from Institutional Ethical Committee.

Patients who met the inclusion and exclusion criteria were randomly selected using simple random sampling. Both eyes of the same

patient were included in this randomized control study.Informed consent was obtained from all subjects after explaining the details of the study.

Patients below 15 years and above 35 years of age, those with anterior segment disease or abnormality, patients already using mydriatics or cycloplegics, all cases of glaucoma, patients with Best Corrected Visual Acuity < 6/60 or near vision <N12, past-ocular surgery, hypertensive patients, diabetic patients, patients on systemic drugs that could affect the pupil or accommodation, patients suspected to have ciliary muscle spasm, and patients with known pseudo exfoliation syndrome (because these patients may have rigid pupil) were excluded.

History: The details of the patient were recorded, including presenting symptoms, history of use of glasses, any previous or coexistent ocular or systemic disease, and use of medications, both systemic and topical.

Pre dilatation Examination: The visual acuity was recorded using an illuminated Snellen's chart, with the patient seated at a distance of 6 meters. The vision was checked with and without correction and with pin hole, and the best corrected visual acuity was noted. The near vision was checked using the Snellen's near vision chart, held at a distance of 33 cm from the patient. Anterior segment examination was performed using an Appa swamy Slit Lamp to rule out any anterior segment disease or abnormality. The resting pupillary diameter was measured at the slit lamp using a millimetre rule (baseline measurement) keeping the magnification at 10 and with minimal illumination intensity. Baseline Blood Pressure and Pulse Rate was measured using sphygmomanometer and Pulse oximeter. Non cycloplegic refraction at baseline was estimated by subjective refraction with the distant target at 6 metre and near target at 33 cm. Near add was given at baseline.

Dilating eye drops: The patients then received the dilating eye drops. Simple randomization was used to decide which eye drop is instilled in the both eyes of the patient.Group A was instilled with Tropicamide 1% in both eyes and Group B was instilled with combination of Tropicamide 0.8% and Phenylephrine 5% in both the eyes by a third person. The process of administering the dilating eye drops was randomized and blinded.

Pupillary diameter: The horizontal pupillary diameter was measured before and at 25 and 45 minutes after instilling the eye drops, using the same procedure as used for baseline measurement.

Cycloplegia: The post cycloplegic refraction was measured manually by subjective refraction at 25 minutes. The near add was increased until the target was seen clearly. Compared to the non-cycloplegic refraction, post cycloplegia all the patients required an increased amount of near add to view the same target clearly. The residual accommodation was measured by increasing the amount of plus add until the target became clear and further increasing the amount of plus add until the target appeared to blur. The difference in the maximum and minimum amount of plus power between which the patient could see the target clearly gave the amount of residual accommodation remaining after cycloplegia.

Blood Pressure and Pulse Rate were measured after 25 minutes of drop instillation by the same method as described earlier.

In both groups of eye drops, any discomfort in respective eyes were noted.

Data analysis: 2 Groups were randomly selected for the purpose of analysis- Group A included eyes that received Tropicamide 1% and Group B included eyes that received the fixed combination of 0.8% Tropicamide with 5% Phenylephrine. The pupillary diameter and residual accommodation were compared between the two groups at each time interval. Cycloplegia was calculated as the difference in the amount of near add required to view the

near target before and after instillation of drops.

Data was analysed using statistical software, and descriptive statistics were presented for demographic and clinical characteristics of the study population. Mean and standard deviation were calculated for continuous variables, and proportions were calculated for categorical variables. Differences in pupillary diameter and residual accommodation between the two groups were analysed using the independent t-test, and the level of significance was set at $p<0.05$.

Results

Table 1: Age and gender distribution of study participants

VARIABLE		GROUP A (T) N(%)	GROUP B (TP) N(%)	TOTAL N(%)
AGE	Group 1 (15-25 years)	33(66%)	29(58%)	62(62%)
	Group 2 (26-35 years)	17(34%)	21(42%)	38(38%)
	Mean age ± SD	23.34 ± 4.93	24.08 ± 6.64	
GENDER	Male	25(50%)	23(46%)	48(48%)
	Female	25(50%)	27(54%)	52(52%)

Table 2: Comparison of the pupillary size between Group A(T) and Group B(TP)at baseline, after 25 minutes and after 45 minutes of instillation of eye drops

Pupillary size (in mm)			
Group (Drug instilled)	Baseline (Mean± SD)	After 25 minutes (Mean± SD)	After 45 minutes (Mean± SD)
Group A (T)	3.02 ±0.10	6.04 ±0.14	7.08 ±0.23
Group B (TP)	3.02 ±0.10	7.03 ±0.23	8.08 ±0.23
P value	1.000	<0.001	<0.001

P<0.05 significant

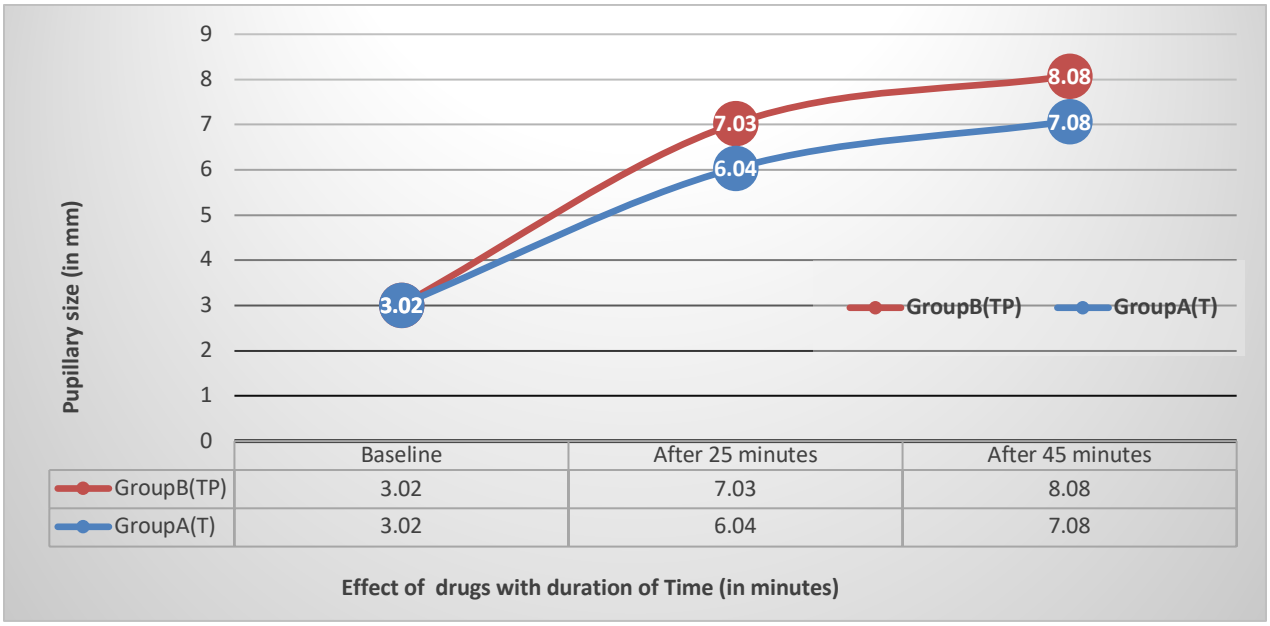

Figure 1: Comparison of the pupillary size (in mm) at Baseline, after 25 minutes and after 45 minutes of eye drop instillation Between Group A(T) and Group B(TP)

Table 3: Changes in spherical equivalent (latent refractive error) after 25 minutes

Spherical Equivalent (in Dioptres) Mean ± SD			
Group (Drug instilled)	**Baseline**	**After 25 minutes**	**Latent error of Refraction (After 25 minutes)**
Group A(T)	-0.79 D ±1.09	-0.58 D ±0.90	-0.21 D ±0.22
Group B(TP)	-0.83 D ±0.66	-0.51 D ±0.41	-0.33 D ±0.27
P value			0.01

P<0.05 significant

Table 4: Changes in Near add (in Dioptres) after 25 minutes (Cycloplegia)

Near Add (in Dioptres) Mean ± SD			
Group (Drug instilled)	**Baseline**	**After 25 min**	**Cycloplegia (After 25 min-Baseline) Mean ± SD**
Group A(T)	0 D ± 0	0.60 D ± 0.12	0.60 D ±0.12
Group B(TP)	0.015 D ±0.07	0.41 D ± 0.12	0.40 D ±0.12
P value			< 0.001

P<0.05 significant

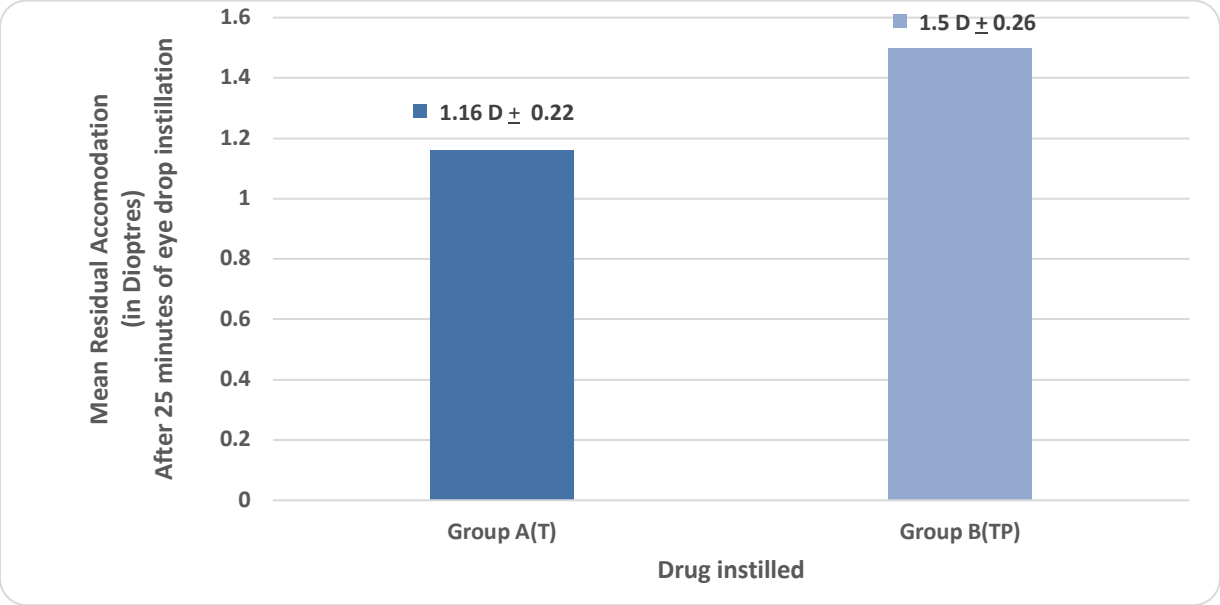

Figure 2. Comparison of Residual Accommodation after 25 minutes of eye drop instillationbetween Group A(T) and Group B (TP)

P <0.001 i.e. significant

Table 5: Effect of age on cycloplegia and residual accommodation in Study Groups

Group (Drug instilled)	Effect of age on cycloplegia and residual accommodation	Group 1 (15-25years) Mean ±SD	Group 2 (26-35years) Mean ±SD	P value
Group A (T)	Cycloplegia (in Dioptres)	0.53 D ±0.15	0.73 D ±0.16	<0.001
	Residual accommodation (in Dioptres)	1.23 D ±0.26	1.02 D ±0.30	<0.01
Group B (TP)	Cycloplegia (in Dioptres)	0.34 D ±0.15	0.48 D ±0.15	<0.001
	Residual accommodation (in Dioptres)	1.68 D ±0.29	1.36 D ±0.29	<0.001

P<0.05 significant

Table 6: Comparison of effect of drug on Blood Pressure and Pulse rate after 25 minutes of eye drop instillation between Group A(T) and Group B (TP)

		Time duration of measurement		
Group (Drug instilled)	**BP(mm ofHg)& PR (beats/min)**	**Before druginstillation Mean ± SD**	**After 25 minutes of drug instillation Mean ± SD**	**P value**
Group A(T)	**Systolic BP**	120.04±8.86	120.08±8.85	0.32
	Diastolic BP	77.12±5.90	77.24±6.01	0.08
Group B(TP)	**Systolic BP**	117.24±5.80	117.36±5.76	0.08
	Diastolic BP	78.24±6.50	78.36±6.45	0.08
Group A(T)	**Pulse Rate**	76.62±4.43	76.70±4.47	0.08
Group B(TP)		75.56±2.26	75.96±2.78	0.001

P<0.05 significant

The study included 100 patients, who were divided into two groups based on age: Group 1 (15-25 years) with 62 patients, and Group 2 (26-35 years) with 38 patients. In Group A (T) who received eye drop 1% Tropicamide, 66% of patients belonged to Group 1 (15-25 years) and rest 34% belonged to Group 2 (26-35 years). While in Group B (TP) who received Eye drop 0.8% Tropicamide and 5% Phenylephrine, 58% of patients belonged to Group 1 (15-25 years) and rest 42% belonged to Group 2 (26-35 years). The mean age of participants was 23.71 ± 5.83 years, with Group A(T) having a mean age of 23.34 ± 4.93 and Group B(TP) having a mean age of 24.08 ± 6.64.

All patients had a best corrected visual acuity (BCVA) of 6/6 and a near vision of N6, except for two patients who had NV (near vision) of N8.

The mean pupillary size at baseline was similar in both groups, with a diameter of 3.02 mm. After 25 minutes of drug instillation, Group B(TP) had a statistically significant larger mean pupillary size than Group A(T), with diameters of 7.03 ± 0.23 mm and 6.04 ± 0.14 mm, respectively ($p < 0.001$). After 45 minutes, Group B(TP) still had a statistically significant larger mean pupillary size than Group A(T), with diameters of 8.08 ± 0.23 mm and 7.08 ± 0.23 mm, respectively ($p < 0.001$).

The study also measured the latent error of refraction, which refers to the difference between the baseline spherical equivalent and the spherical equivalent required by patients after 25 minutes of drop instillation. Both groups showed a reduction in spherical equivalent required, with Group A(T) having a statistically significant higher difference in the change in refraction readings than Group B(TP) ($p = 0.01$). The mean latent error of refraction was -0.21 ± 0.22 D for Group A(T) and -0.33 ± 0.27 D for Group B(TP). The mean cycloplegia for Group A(T) was 0.60 ±0.12D and for Group B(TP) was 0.40±0.12D. The difference in the near add between the two groups after 25 minutes was statistically significant, with a higher near add required for Group A(T) ($p < 0.001$).

The residual accommodation left after 25 minutes of drop instillation was also measured, with Group B(TP) having a statistically significant higher mean residual accommodation than Group A(T) ($p < 0.001$). The mean residual accommodation was 1.16 ± 0.22 D for Group A(T) and 1.5 ± 0.26 D for Group B(TP).

In addition, the study found that the amount of cycloplegia induced increased with increasing age, with Group 2 having a higher mean cycloplegia than Group 1 ($p < 0.001$). On the other hand, the residual accommodation decreased with increasing age, with Group 1 having a higher mean($p < 0.001$).

The study measured the effects of a drug instillation on blood pressure and pulse rate in two groups, Group A(T) and Group B(TP).

In Group A(T), the mean systolic blood pressure before drug instillation was 120.04 ± 8.86 mmHg and after 25 minutes of drug instillation, it slightly increased to 120.08 ± 8.85 mmHg. The mean diastolic blood pressure before drug instilled was 77.12 ± 5.90 mmHg and after 25 minutes of drug instillation, it slightly increased to 77.24 ± 6.01 mmHg.

While in Group B(TP),mean Systolic Blood Pressure before drug instilled was 117.24 ± 5.80 mmHg and after 25 minutes of drug instillation it slightly increased to 117.36 ± 5.76 mmHg in Group B(TP). Mean Diastolic Blood Pressure before drug instilled was 78.24 ±6.50 mmHg and after 25 minutes of drug instillation slightly increased to 78.36 ± 6.45 mmHg in Group B(TP). However, there was no statistically significant difference in blood pressure after 25 minutes of drug instillation in either study group (Group A(T) and Group B(TP)). In Group A(T), Mean Pulse Rate before drug instilled was 76.62 ± 4.43 bpm and after 25 minutes of drug instillation increased to 76.70 ± 4.47. The increase in pulse rate was only mild and clinically and statistically not significant with a p value > 0.05.

In Group B(TP), Mean Pulse Rate before drug instilled was 75.56 ± 2.26 bpm and after 25 minutes of drug instillation increased to 75.96 ± 2.78. There was a statistically significant increase in pulse rate in Group B(TP) after drug instillation with a p value < 0.05.

Discussion

This hospital based analytical cross-sectional study aimed to evaluate the efficacy and safety of 1% Tropicamide alone versus a combination of 0.8% Tropicamide and 5% Phenylephrine for mydriasis and cycloplegia. The results showed that Group B(TP), which received a combination of Tropicamide 0.8% and Phenylephrine 5%, had a significantly larger mean pupillary size than Group A(T), which received Tropicamide 1% alone, after 25 and 45 minutes of drug instillation. These findings are consistent with previous studies that have demonstrated the superior mydriatic effect of Phenylephrine when used in combination with Tropicamide.

A study by Mishra *et al*.(2013) compared the mydriatic effect of Tropicamide 0.8% and Phenylephrine 5% combination with Tropicamide 1% alone and found that the combination group had significantly larger pupil diameter than the Tropicamide group.[4] Similarly, another study by Reddy *et al*. (2017) showed that a combination of Tropicamide and Phenylephrine produced a larger pupil size than Tropicamide alone.[5] The larger pupil size in the combination group is attributed to the fact that Phenylephrine causes contraction of the dilator muscle in addition to the relaxation of the constrictor muscle by Tropicamide, resulting in a more pronounced dilation effect.Also the evidence provided by present study that a single drop of fixed drug combination is sufficient to produce a well sustained pupillary dilatation further confirms the results of previous studied highlighting the adequacy of a single dose regimen for pupillary dilatation [6-10]. The results of the present study suggest that Tropicamide alone uncovered significantly higher mean latent error of refraction as compared to the Tropicamide/Phenylephrine combination eye drops. This finding is contrary to the results of a study conducted by Kumar S. *et al*, where no statistically significant difference was found in the change in refraction readings (latent error) over time between the two groups [11].

We hypothesize that the observed difference between our studyand Kumar S. *et al* study may be explained by the fact that cycloplegia induces a significant decrease in lens thickness and causes backward movement of the lens, which increases Spherical aberration. This increased Spherical aberration might be responsible for the decreased Spherical equivalent accepted by patients after 25 minutes of drop instillation. Additionally, the better cycloplegic effect observed in Group A(T) with 1% Tropicamide may have led to more latent error refraction being uncovered by Group A(T) drop.

Our study found that Group A (T), which received 1% Tropicamide, required a significantly higher near add compared to Group B (TP) after 25 minutes of drop instillation.A previous study by Kumar S. *et al*. (2016), found a marginally higher near add required by the group that received Tropicamide 1% alone but the difference was not statistically significant (p=0.08) [11]. The reason for this difference in result is not clear and may be due to difference in study population.

In our study,the adequacy of drug as a cycloplegic was evaluated by measuring the amount of residual accommodation remaining after its use. Residual accommodation of <2 D is considered acceptable by most of the authors. [12,13] The values of mean residual accommodation were lower in the Group A(T), this difference was statistically significant ($p < 0.001$)) with both groups well within the limits of 2 D of residual accommodation agreed upon by different authors. So, in this study,it was observed that the combination drop which contains lesser concentration of tropicamide (0.8%) is less effective as cycloplegic as 1% tropicamide alone due to higher residual accommodation persists. This finding is consistent with previous studies (Yadav *et al*., 2014; Ikaunieks *et al*., 2019) that have shown higher concentrations of Tropicamide lead to greater cycloplegic effects [14,15].

The results of our study that amount of cycloplegia increased with increasing age and residual accommodation decreased with increasing age in both the study groups, are consistent with previous studies that have shown that younger individuals have a higher accommodative tone, which results in higher residual accommodation after cycloplegia. However, despite the higher residual accommodation in younger individuals, the cycloplegia was still considered adequate for refraction, as the mean residual accommodation in each group was less than 2 D.Kumar S *et al*. also found a statistically significant difference in residual accommodation between younger and older age groups [11]

On investigating the effects of topical administration of these eye drops on blood pressure and pulse rate in adults, it was found that a mild and statistically insignificant increase in both mean systolic and diastolic blood pressure in Group A (T) and Group B (TP) after 25 minutes of drug instillation. However, there was a clinically and statistically significant increase in pulse rate after 25 minutes of drug instillation in Group B (TP) compared to Group A (T). This could be explained by the vasoconstrictor effect of phenylephrine, which could narrow the blood vessels and increase blood pressure and pulse rate. The increase in pulse rate was more pronounced with the combination of tropicamide and phenylephrine, possibly due to the combined effect of both drugs. However, our study did not observe any significant effect on blood pressure, which may be attributed to the lower concentration of phenylephrine (5%)used in our study.

In a study conducted by Motta MS *et al*., the effect of phenylephrine on blood pressure and heart rate were studied before and after use of phenylephrine 2.5%. In this study, statistical analysis did not show statistical difference before and after the drug application [16].

In contrast, Alpay A. *et al* conducted a study to determine the side effects of phenylephrine 2.5% and tropicamide 0.5% combination in preterm infants. The study found no any significant change in blood pressure and in their study, there was decrease in average heart rate [17]. Our study didn't coincide with their findings as age group was not similar in both the studies.There was only mild burning sensation observed in all patients irrespective of type of drop instillation immediately after drop instilled which lasted forless than one minute. No other ocular side effects were observed in this study.

Conclusion

The study found that the combination group had a significantly larger mean pupillary size than the Tropicamide alone group. Tropicamide alone uncovered significantly higher mean latent error of refraction and had higher cycloplegic effect as compared to combination group. The study also found that increasing age led to increased cycloplegia and decreased residual accommodation in both groups. The study concluded that the fixed drug combination is sufficient to produce well-sustained pupillary dilation with a single drop, but caution must be exercised when administering the combination of tropicamide and phenylephrine as it can cause an increase in pulse rate.

Implications

The study findings may help ophthalmologists make more informed decisions about the choice of medication for mydriasis and cycloplegia, taking into account both efficacy and potential side effects.

The study provide evidence to support or refute the use of the combination of Tropicamide and Phenylephrine for mydriasis and cycloplegia.

The study may have implications for the development of guidelines and protocols for the use of mydriatic and cycloplegic eye drops in clinical practice.

Strength and Limitation

The study used a simple random sampling method to minimize the risk of selection bias.

But the results of the study should be assessed in the background of following limitations:

The study only included patients aged between 15 and 35 years, which may limit the generalizability of the results to other age groups. The study did not include patients with specific conditions or diseases, such as glaucoma, which may require different treatment protocols. Also, the study is conducted in a single hospital, which may limit the generalizability of the results to other settings.

Future Directive

This study can be replicated in larger sample sizes or with different age groups to further validate the findings. Future studies should also incorporate patient-reported outcomes such as satisfaction and comfort during the procedure to better understand the patient experience and identify areas for improvement. Further studies could evaluate the effects of these medications on the accuracy of other diagnostic tests such as visual field testing or optical coherence tomography.

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