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Comparison of Effect of Single Drop of Tropicamide 0.8% and Phenylepherine 5% versus Multiple Drops on Cycloplegia and Near Point of Convergence (NPC).

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ABSTRACT

The quality of an intraocular examination for intra-ocular surgeries like cataract surgery, depends on adequate pupil dilatation and for refraction depends on the cycloplegia attained by the drug. Mydriatics are also very commonly used as cycloplegic drug in early presbyopes and in adults attending ophthalmologic OPD for the asthenopic symptoms for detection of latent refractive errors. Strong cycloplegic drugs retain their effect for longer duration and hence not very acceptable to patients as it hampers their routine daily activities, hence drugs with shorter duration of action and acceptable cycloplegia is desired in adults requiring refraction assessment for asthenopic symptoms. To assess the cycloplegia and convergence on single and multiple applications of the drug.2)To assess the patient for any adverse drug reactions on application of the drug. A hospital based randomised controlled trial of minimum 100 cases in each group,who presented to the department of Ophthalmology ,Sri Siddhartha Medical College,Tumkur between November 2011 to June 2013 were taken. After recording the demographic data, a brief systemic examination for, base line pulse and blood pressure were done. Pupils were assessed for direct and indirect light reflexes and the initial pupil size was recorded using pupil gauge. Accommodation and convergence were assessed using Livingstone's gauge/RAF rule. The patients were randomly allocated into 2 groups, group A was administered single drop and group B was administered multiple applications (at intervals of 10 minutes for a total of 40 minutes) of a combination of 0.8% Tropicamide and 5% Phenylephrine. The pulse, blood pressure, pupil size, convergence and cycloplegia were assessed every 10 minutes for a total duration of 40 minutes. The near point of accommodation after 20 minutes was found to be also significantly lower in the multiple group as compared to the single group(23.95 ± 2.29 cm after 20 minutes in single group; 23.16 ± 2.30 cm after 20 minutes in multiple group; p-value 0.016 was significant). But the final near point of accommodation after 40 minutes in both the single and multiple applications groups were similar(34.35 ± 1.77 cm in single group; 34.49 ± 1.53 cm in multiple group; p-value not significant). The increase in the near point of convergence after 40 minutes was comparable both the groups , but there was no difference in single vs multiple group. The increase in the heart rate was not found to be significant in both the groups. The increase in the systolic blood pressure was not significant in both the groups. Tropicamide- phenylepherine combination drop can be an effective cycloplegic in adults, whose accommodation reserve are weaker compared to children. The effect of cycloplegia don't differ with the number of instillations. Also no systemic adverse effects were noted with the drops .

Keywords: Tropicamide , Phenylepherine ,Cycloplegics, Convergence, Accomodation

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INTRODUCTION

The quality of an intraocular examination for refraction as well as intra-ocular surgeries like cataract surgery, depends on adequate pupil dilatation [1].

Mydriatics are also very commonly used as cycloplegic drug in early presbyopes and in adults attending ophthalmologic OPD for the asthenopic symptoms for detection of latent refractive errors. Parasympathetics as well as sympathomimetic drugs have been used to dilate the pupil.

The most desired effect of these cycloplegic agents is their effect on the ciliary muscles of the eyes, which are paralyzed to bring about relaxation or a complete elimination of accommodation, that is, cycloplegia.

Cycloplegia is the paralysis of the ciliary muscles achieved by blocking the muscarinic receptors normally stimulated by the release of acetylcholine from the nerve endings of the parasympathetic system .Cycloplegia is always accompanied by mydriasis (although mydriasis is not always accompanied by cycloplegia [2]. Cycloplegic drugs reduce accommodation thus making latent refractive errors manifest [3,4].

A satisfactory prescription for glasses may be given only after accurate refractive assessment of the eye. The punctum remotum, or the far point of the eye, is the conjugate focus of the retina when the eye is in a non-accommodative state. Clinical methods to suspend accommodation during the examination are needed. This can be achieved in one of two ways:

- By inserting stronger convex lenses known as the “fogging technique”; by paralyzing the accommodation with drugs, “cycloplegia.
- Blockade of the cholinergic system dilates the pupil (mydriasis) and relaxes the ciliary muscle, decreasing accommodation (cycloplegia)

The cilliary muscle may have a minor adrenergic innervation, with stimulation decreasing accommodation.

Accommodation Reflex

Accommodations include (l) convergence of the eyes, (2) thickening of the lenses, and (3) pupillary constriction. Convergence keeps the object focused on the fovea for maximum visual acuity. As the object is brought closer, light rays become less parallel, and the refractive power of the lens must be increased to focus the image on the retina. The lens becomes more spherical, thereby increasing its refractive power. In order to increase the depth of focus the pupils constrict [5].

1811 when William Wells, a London oculist, discovered that a patient whose pupils were dilated with Atropine had partial ptosis and a failure of accommodation. The refractive state also changed from slightly myopic to slightly hyperopic [6].

Cycloplegic Agents

Cycloplegic agents are drugs that act by antagonizing the muscarinic action of acetylcholine. They do so by blocking its action at structures innervated by postganglionic parasympathetic nerve fibres. These agents paralyse the constrictor pupillae as well as the ciliary muscle, causing mydriasis as well as cycloplegia [7].

For many years, atropine was the only cycloplegic agent available. To bring about full cycloplegia in children, it had to be instilled two or three times daily for three days prior to cycloplegic refraction. The resulting cycloplegia persisted for seven to ten days and the accompanying mydriasis lasted as long as two weeks [8].

Homatropine is a semi-synthetic alkaloid, the cycloplegic effect begins in a matter of 45-60 minutes [9].

Cyclopentolate (cyclogyl) is a short acting cycloplegic agent available in 0.5 and 1.0 percent solutions. With this agent, cycloplegia occurs within 30-45 minutes and persists for up to 24 hours. Even though it does not yield as complete cycloplegia in children as atropine, it is considered a suitable alternative to atropine for children, even under the age of six. Reports of central nervous system effects following the use of cyclopentolate include confusion, ataxia and personality changes [9].

Tropicamide (Mydriacy I) is also a short acting cycloplegia available in 0.5 and 1.0 percent solutions. For young adults, three or four drops of the 1.0 percent solution, separated by a few minutes, will bring about full cycloplegia, and recovery occurs in two to six hours. Davies (1989) considers tropicamide inadequate for producing cycloplegia in children [9,10]. According to Lyle and Hopkins (1977), reports of adverse reactions to tropicamide are made conspicuous by their rarity. In addition to its use as a cycloplegic, tropicamide is widely used as a mydriatic agent [10].

Choice of a Cycloplegic Agent

In children below the age of six years, complete cycloplegia can be obtained only with the use of atropine. However, the use of atropine is attended by a number of complications.

When an agent other than atropine is used for cycloplegic refraction, it is not considered necessary to subtract a “tonus allowance” as it is when atropine is used. On the basis of Davies (1989) report, that twenty patients between the ages of 10 and 14 who were refracted under tropicamide had an average amount of residual accommodation of 3.56D, it is recommended that cyclopentolate (1 percent) be used for children. Tropicamide, however, will induce an adequate cycloplegic effect in adults.

Indication for Cycloplegic Refraction

Among the diagnostic pharmaceutical agents that ophthalmologists use, cycloplegic agents are indicated in far fewer cases than either mydriatic agents or anesthetics. Mydriatics are used frequently by practitioners who use binocular indirect ophthalmoscopy and fundus photography, while topical anesthetics are used routinely by practitioners who perform applanation tonometry and gonioscopy. Cycloplegic refraction is in fact necessary for only a small percentage of patients [11].

Commonest indications being, 1) When a child (often a pre-scholar) is seen with a convergent strabismus, and 2) For young adults between the ages of 16 and 40, latent hyperopia presents with asthenopic symptoms.

Tropicamide (1 percent) is considered to be the best cycloplegic agent because it has virtually no side effects,especially for adults.

Cycloplegics are also used in 1) ciliary spasm 2) uveitis 3) occlusion

Factors Affecting the Choice of a Cycloplegic

Age: the amplitude of accommodation in children is always greater than that of adults.

Pigmentation of the Iris: it is quickly evident to an examiner with much clinical experience that greatly pigmented irides, such as are seen in non-Caucasians, will dilate with greater difficulty than the lightly pigmented eye.

Occupation: excluding the young child, in using cycloplegic agents in therapeutic for diagnosis the more committed or in-demand an individual is, the greater the need for an agent with rapid recovery.

Tropicamide

Tropicamide thus belongs to the parasympatholytic drug group and is an antimuscarinic agent that acts as a competitive antagonist to acetylcholine and other muscarinic drugs. The actions of acetylcholine are

inhibited by tropicamide at the structures innervated by the postganglionic cholinergic nerves of certain smooth muscles.

Tropicamide and all others in the antimuscarinic class block the action of the sphincter muscle of the iris and the ciliary muscles of the lens to cholinergic stimulation, thereby dilating the pupil and inhibiting accommodation (cycloplegia).

When a 0.5 percent or a 1 percent solution of tropicamide is used, mydriasis is rapid in onset reaching its peak in 15– 30 minutes with a return to normal occurring in 8–9 hours. Tropicamide's cycloplegic action is relatively weak reaching its maximum effect after 25 minutes and with full amplitude having returned after 6 hours (Vale and Cox, 1984) [10].

Precautions

- Tropicamide should not be used in patients with a narrow angle glaucoma since it may raise intra-ocular pressure and precipitate an acute attack.
- As with other antimuscarinic agents, tropicamide should be used with caution in conditions characterised by tachycardia such as thyrotoxicosis, heart failure, and in cardiac surgery where it may further accelerate the heart rate. Care is required in patients with acute myocardial infarction as ischaemia and infarction may be made worse.

Adverse Reactions

Systemic side effects

BODY: Anaphylaxis

CVS: Transient brachycardia followed by tachycardia, with palpitations and arrhythmias.

CNS: Drowsiness and sedation, inability to concentrate and fatigue, psychotic reactions and behavioural disturbances – more common in children than adults.

RESP: Dryness of the mouth with difficulty in swallowing and talking, thirst, reduced bronchial secretions, bronchospasm.

GIT: Difficulty in micturition, as well as reduction in the tone and motility of the gastro-intestinal tract leading to constipation. Occasionally vomiting may occur.

SKIN: Rash erythematous and pruritis. Flushing and dryness of the skin, increased sweating.

OCULAR: Photophobia with or without corneal staining, significant increases in intraocular pressure, corneal irritation, smarting eyes, severe oedema of the eyelids and rhinitis. Dilation of pupils (mydriasis) with loss of accommodation (cycloplegia) and photophobia, risk of inducing angle closure where prior history, possibility of elevating intra-ocular pressures.

Phenylephrine

Phenylepherine is an α adrenergic agonist. It contracts iris dilator muscle and the smooth muscle of the conjunctival arterioles, causing blanching. Maximum dilatation is 45 to 60 minutes after instillation. Recovery on average is 3 hours for 2.5% drops and 6 hours for 10% drops. Increased drug concentrations gives more rapid onset but the maxium effect may still take up to 60 minutes [12].

Phenylephrine side effects and cautions

Local (ocular) effects; blurring, watering, photophobia, keratitis and rebound miosis (small pupil). Systemic (whole body) effects; short term raised blood pressure, headache, increased heart rate (tachycardia) and blanching of the skin.

Contraindications to use of 10% phenylephrine; elderly patients with preexisting cardiac disease. Patient taking mono-amine oxidase inhibitor (MAOIs) antidepressants, tricyclics or methyldopa. Side effects are more likely with the higher concentrations.

Tropicamide and phenylephrine combination eye drops are widely used for mydriasis in routine ophthalmoscopic examinations [1,3, 13]. and prior to cataract surgery to achieve maximal pupil dilation [4]. Phenylephrine hydrochloride, a sympathomimetic agonist, is a strong alpha1-receptor stimulant with little or no beta-receptor effect. Cardiovascular actions of phenylephrine include vasoconstriction of the systemic, pulmonary, and coronary arteries. Adverse systemic reactions have been reported following topical application of 10% phenylephrine like elevated blood pressure, tachycardia, reflex bradycardia, cardiac arrhythmias [12,14].′ Tropicamide, on the other hand, is a parasympathomimetic antagonist that causes mydriasis and cycloplegia [11]. It is devoid of vasopressor effect [11].

The RAF (Royal Air Force) Rule provides a binocular gauge to measure Objective and Subjective Convergence as well as Accommodation in 1 mm increments. The RAF Rule consists of a 50 cm long rule with a slider holding a rotating four-sided cube. Each side has a different target. The first has a vertical line with a central dot for convergence fixation. The others provide a limited number of lines of near reading examples [14].

A rest is provided for the cheek to insure consistency and proper height for the patient. Some studies have shown greater consistence of the NPC when measured with the RAF Rule compared to using a pencil or finger.

This instrument is used for determining the objective and subjective convergence points, examining the accommodation and determining the master eye. The RAF Rule is useful for both diagnosis and treatment.

The instrument is made of metal and plastic; it is 50 cm. long and is marked on the top in centimetres, and on the two sides in dioptres and the corresponding age groups.

On a metal slide is carried a quadrilateral which can be rotated to present on each of its four washable white plastic faces the following optical tests:

(a) Reduced Snellen test type which subtends the same angle at the eye at 35 cm. as the test type subtends at 6 metres.
(b) "Times Roman" type face recommended by the Faculty of Ophthalmologists (Law, 1951) presented in four lines: N.5, N.8, N.O0, and N.12.
(c) Photographic reproduction of a section of the G.P.O. Telephone Directory.
(d) Vertical line and central dot for convergence fixation.

The new rule was made 50 cm. in length for two reasons:

(1) Many presbyopes with an indifferent power of convergence prefer to read at a distance of some 40 cm.
(2) The angle of 250 from the eye can be easily determined, by a point at the end of a rule 23-3 cm. long (tan 250 x 50) held at right angles to the end of the rod.

MATERIALS AND METHODS

- A Randomized controlled study comparing single(minimum 100 cases) versus multiple(minimum 100 cases) applications of combination of tropicamide and phenylephrine eye drops in patients attending the Out Patient Department of Ophthalmology in Sri Siddhartha Medical College and Hospital, Tumkur, between November 2011 to June 2013.
- After taking informed consent ,detailed history regarding patients name, age, sex, occupation, address, presenting symptoms, duration, progression, were recorded. The patient was also enquired about his past history, personal history and family history.
- Accommodation and convergence were assessed using Livingstone's gauge/RAF rule.

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- The patients were randomly allocated into 2 groups, group A was administered single drop and group B was administered multiple applications (at intervals of 10 minutes for a total of 40 minutes) of a combination of 0.8% Tropicamide and 5% Phenylephrine.
- The pulse, blood pressure, pupil size, convergence and cycloplegia were assessed every 10 minutes for a total duration of 40 minutes.
- The patients fundus was examined with a direct ophthalmoscope, and their retinoscopy values were recorded using a streak retinoscope

OBSERVATION

The mean age of the participants in my study was 25.3 ± 2.83 years in the single application group and 24.83 ± 2.66 years in the multiple application group(range 20-40 years).48.5% were in the 20-24 years category,44.5% in the 25-29 years category, 7% in the 30-34 years category and none in the 35-40 years category with a mean age of 25.07 years(minimum of 20 years and maximum of 34 years).

Table 1: Age and sex distribution

Age Group	Male	Female	Total	
			Number	%
20 - 24 years	41	56	97	48.5
25 - 29 years	57	32	89	44.5
30 -34 years	7	7	14	7
	105 (52.5%)	95 (47.5%)	200	

The sex distribution in my study was 47.5% females and 52.5% males.

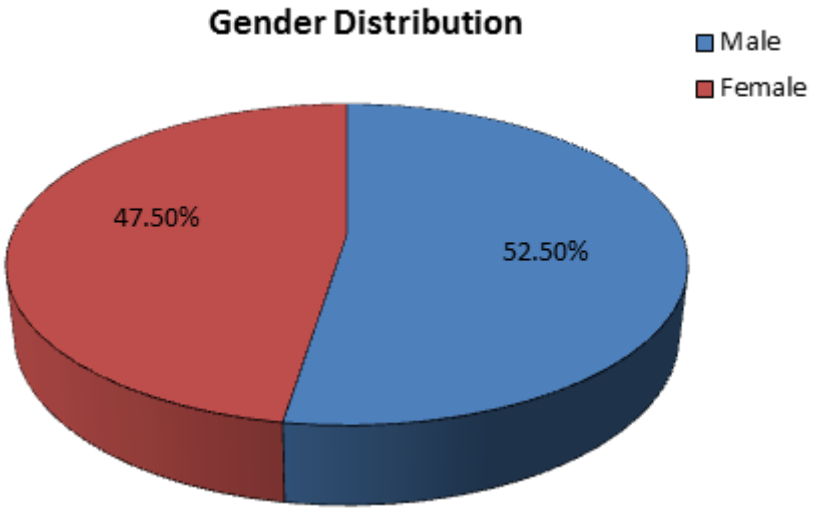

Table 2: The baseline data of all patients in both the groups.

	Single Application	Multiple Application
Number of Patients	100 (200 eyes)	100 (200 eyes)
Male / Female	52 / 48	53 / 47
Age, in years, Mean ± SD	25.3 ± 2.83	24.83 ± 2.66
Pupil size mean ± SD (in mm)	3.02 ± 0.14	3.04 ± 0.2
Pulse mean	70.80 ± 5.55 / min	71.58 ± 5.40 / min
Blood Pressure, mean systolic	118.66 ± 5.07 mm Hg	119.26 ± 2.75 mm Hg
Blood Pressure, mean Diastolic	76.24 ± 3.86 mm Hg	76.78 ± 4.36 mm Hg

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Table 3: The effect on NPA in each group at various time intervals.

	NPA, mean ± SD (in cm)		T – test
	Single Application	**Multiple Application**	**P – value**
Baseline	12.13 ± 0.86	11.83 ± 1.02	0.025#
10 mins	17.80 ± 1.72	17.33 ± 1.69	0.469*
20 mins	23.95 ± 2.29	23.16 ± 2.30	0.016#
30 mins	29.74 ± 1.77	29.88 ± 2.51	0.649*
40 mins	34.35 ± 1.77	34.49 ± 1.53	0.550*

p-values are significant. * p-values are not significant.

Table 4: The effect on NPC in each group at various time intervals.

	NPC, mean ± SD (in cm)		T – test
	Single Application	**Multiple Application**	**P – value**
Baseline	7.77 ± 1.32	7.63 ± 1.08	0.414*
10 mins	8.08 ± 1.44	7.95 ± 1.21	0.490*
20 mins	8.58 ± 1.64	8.34 ± 1.33	0.257*
30 mins	9.01 ± 1.72	8.87 ± 1.35	0.523*
40 mins	9.27 ± 1.98	9.05 ± 1.45	0.371*

* p-values are not significant.

Table 5: The effect on systolic blood pressure in each group at various time intervals.

	Systolic Blood pressure, mean ± SD (mm Hg)		T – test
	Single Application	**Multiple Application**	**P – value**
Baseline	118.66 ± 5.07	119.26 ± 2.75	0.300*
10 mins	119.02 ± 5.04	119.94 ± 2.85	0.114*
20 mins	120.18 ± 5.27	121 ± 2.82	0.172*
30 mins	121.90 ± 8.57	122.18 ± 3.06	0.792*
40 mins	121.52 ± 5.4	122.56 ± 3.27	0.101*

Table 6: Adverse reaction in single and multiple group

	Adverse Reaction	No adverse reaction
Single drug group	0	100
Multiple drug group	0	100

DISCUSSION

The mean age of the participants in my study was 25.3 ± 2.83 years in the single application group and 24.83 ± 2.66 years in the multiple application group(range 20-40 years).48.5% were in the 20-24 years category,44.5% in the 25-29 years category, 7% in the 30-34 years category and none in the 35-40 years category with a mean age of 25.07 years (minimum of 20 years and maximum of 34 years).

The sex distribution in my study was 47.5% females and 52.5% males.

In this study, we compared the cycloplegia attained in an adult with Tropicamide phenylepherine combination drops, in single drops versus multiple drops and evaluated for any systemic adverse reaction of the drops.

The baseline near point of accommodation was significantly lower in the multiple group as compared to the single group(12.13 ± 0.86 cm baseline near point of accommodation in single group; 11.83 ± 1.02 cm baseline near point of accommodation in multiple group; p- value 0.025 was significant). The near point of accommodation after 20 minutes was found to be also significantly lower in the multiple group as compared to the single group(23.95 ± 2.29 cm after 20 minutes in single group; 23.16 ± 2.30 cm after 20 minutes in multiple group; p-value 0.016 was significant). But the final near point of accommodation after 40 minutes in both the

single and multiple applications groups were similar(34.35 ± 1.77 cm in single group; 34.49 ± 1.53 cm in multiple group; p-value not significant).

The baseline near point of convergence, near point of convergence every 10 minutes and the near point of convergence after 40 minutes in both the groups, the single application and the multiple application groups was similar (7.77 ± 1.32 cm baseline in single group; 7.63 ± 1.08 cm in multiple group; p-value not significant and 9.27 ± 1.98 cm after 40 minutes; 9.05 ± 1.45 cm after 40 minutes; p-value not significant). Moreover the increase in the near point of convergence after 40 minutes was not significant in both the groups.

The effect of the drug was studied on the near point of accommodation (cycloplegic effect) as well as near point of convergence in both the groups. It was found that pupillary dilatation was associated with cycloplegia in both the groups and the cycloplegic effect was comparable. However the increase in the near point of convergence was not significant in both the groups.

Hamasaki I et al conducted a study to evaluate the cycloplegic effect of mixed eye drops containing 0.5% tropicamide and 0.5% phenylephrine in myopic children, and to determine whether their efficacy was associated with their clinical characteristics. They found that the insignificant magnitude of residual accommodation indicated that the mixed eye drop is an acceptable and useful cycloplegic agent in Japanese schoolchildren with a wide range of myopic refractive errors [15].

Zhu X et al studied the effect of 0.5% Tropicamide/0.5% phenylepherine drops and made inter eye refractive comparison in Chinese adults and concluded that accommodation was relaxed by the mixed drops in myopic adults , the changes of refraction due to cycloplegia were not well correlated , probably due to ocular dominance [16].

Manny R E et al studied the cycloplegic effect of Tropicamide 1% eyedrops in myopic children and its variability compared to age, gender, iris colour ethnicity and magnitude of refractive error and concluded that tropicamide is an effective cycloplegic agent in myopic children [17].

Egashira SM et al did a double masked study Comparing the Cycloplegic effect of tropicamide 1% and cyclopentolate 1% in 20 non strabismic, non-Amblyopic, children aged 6-12 year and suggested that though tropicamide is as effective cyclopentolate in inhibiting accommodation, it is nevertheless a useful cycloplegic agent for, measuring the distance refractive error of low to moderate Hyperopia in school children [18].

In our study the baseline systolic blood pressure, systolic blood pressure every 10 minutes and the systolic blood pressure after 40 minutes was similar in both the groups(118.66 ± 5.07 mm Hg baseline in single group; 119.26 ± 2.75 mm Hg baseline in multiple group; p-value not significant and 121.52 ± 5.4 mm Hg after 40 minutes in single group; 122.56 ± 3.27 mm Hg after 40 minutes in multiple group; p-value was not significant). The increase in the systolic blood pressure was not significant in both the groups.

Motta M et al compared the cardiovascular effects of phenylephrine 2.5% versus phenylephrine 10%. Their results corroborate the finding that one single drop of either 2.5 or 10% has no effect on blood pressure and, when 1% tropicamide is combined, satisfactory pupil dilation is achieved [19].

In a study by Bhatia et al mild rise in systolic BP about 3 mm of Hg (SD 19.03) and 1 mmHg in Diastolic (SD 11.5) was seen, and hence they concluded though not much change is seen in normotensive patients, care should be taken in using 10% phenylepherine in hypertensives [2].

Chin et al reported significant increase in BP after instilling 2.5% or 10% phenylepherine in preoperative patient, However their study does not take into account the effect of anxiety and adrenalin mixed in local anaesthetic [21].

SUMMARY

200 outpatients were randomised into 2 groups- a single application group of 100 patients and multiple application group of 100 patients. Statistical analysis shows that cycloplegia in both the groups and

the cycloplegic effect was comparable. However the increase in the near point of convergence was not significant in both the groups. In this study, the effect of the combination drug of tropicamide and phenylephrine on pulse and blood pressure(systolic and diastolic) was not found to be significant. Moreover, no adverse drug reactions were noted in any of the study participants.

CONCLUSION

Thus we can conclude that Tropicamide phenylepherine combination drop can be an effective cycloplegic in adults, whose accommodation reserve are weaker compared to children. The effect of cycloplegia did don't differ with the number of instillations. Also no systemic adverse effects were noted with the drops.

Thus a single drop of combination of tropicamide and phenylephrine can be as efficacious as using multiple drops of the same for routine pupillary dilatation for fundoscopic examination,for producing cycloplegia as well as preoperatively before cataract surgery.

This can lowers the risk of adverse reactions which have been reported with the use of phenylephrine and is thus safer ,as compared to multiple applications.

It also reduces the requirement of the man power required for Carrying out dialatation in the OPD.

Moreover this can significantly reduce the cost as well as the need for manpower for instillation of drops.

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