

## Individual and Additive Mydriatic Effect of Tropicamide with Phenylephrine and Flurbiprofen in Diabetic Patients

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**Abstract:** Diabetes mellitus is a chronic metabolic disorder and one of its major complications is diabetic retinopathy. For ophthalmological screening of diabetic retinopathy, we use mydriatic drugs for pupil dilation. As per the literature review, there is no clinical data available in Indian population for the combination of Tropicamide and Flurbiprofen. Hence, the present study was carried out in an attempt to study the possible mydriatic effect of selected combination in diabetic patients. A randomized controlled trial was conducted in diabetic patients. Patients were divided into three groups and a sample size of fifty was included by calculation in each group. Tropicamide was instilled in all the groups, Phenylephrine and Flurbiprofen was instilled in groups 2 and 3 respectively. The mean pupil dilation using Tropicamide and Flurbiprofen combination was higher ( $P < 0.01$ ) compared with Tropicamide alone and in combination with Phenylephrine. A new combination of Tropicamide (muscarinic receptor antagonist) and Flurbiprofen (non-steroidal and anti-inflammatory drug) was found to be more effective in bringing maximal dilation of pupil in diabetic patients. Further studies with different combinations and concentrations may be carried out.

**Key words:** Diabetes • Mydriasis • Tropicamide • Phenylephrine • Flurbiprofen

### INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder with hyperglycemic state. Either type of diabetes 1, 1.5 or 2 may lead to diabetic retinopathic condition if blood sugar level is poorly controlled. Since the entry of glucose molecule into a retinal cell is independent of insulin, patients of poorly controlled diabetes are more prone to get diabetic retinopathy [1, 2]. Hence all the diabetologist advise their patients for routine eye checkup. Mydriasis or pupil dilation is an essential component of ophthalmologic tests and treatments. The level of dilation of pupil depends on the sphincter and dilator muscle of the pupil which is controlled by parasympathetic and sympathetic nerves respectively [3, 4]. Meticulous examination of lens, vitreous and retina requires adequate pupillary dilation. An ideal mydriatic should have a sudden onset of action and quick recovery and mainly not cause discomfort or side effects.

Literature review reveals different controversies when combination of two different drugs is used. Some have reported better dilation with combination and some have reported there is no such significance exists with combination [5, 6]. The current study is an attempt to examine the combination of two drugs of different mechanism of action to achieve better pupil dilation in diabetic patients.

### MATERIALS AND METHODS

**Study Protocol and Recruitment:** A randomized prospective study was undertaken at Ophthalmology department in SRM Medical College hospital and research center, Chennai. Approval of the protocol and study documents was obtained from Institutional Ethical Committee (135/IEC/2011) before study commencement. The study was well explained to all patients enrolled in the study and all of them gave written consent form.

The study was conducted over a period of nine months from March 2011 to November 2011. The selected patients were either men or women aged  $\geq 18$  years and were diagnosed as diabetic patient by diabetologist and referred to ophthalmologist for screening their diabetic retinopathic condition. Non diabetic patients and patients who expressed unwillingness to participate in the study were excluded from the study.

**Hypothesis and Sample Size Calculation:** Pupil size greater than 6mm was considered clinically to be effective for any ophthalmological screening [7]. By keeping this in mind and based on literature review the hypothesis of this study is that Tropicamide and Flurbiprofen combination may bring better mydriasis than the routine drugs. The sample size was calculated considering the maximal pupil dilation as the primary efficacy parameter. An  $\alpha$  error of 0.05 and 90% as power of the study will be able to reject the null hypothesis using paired test and thus fifty patients must complete their study in each group.

A total of one hundred and fifty patients were assigned into three groups using computerized random allocation software. Age, gender, duration of diabetes and other demographic details were noted in data entry form. Group 1 (n=50) was treated with Tropicamide (1%); group 2 (n=50) was treated with Tropicamide and Phenylephrine (5%) and group 3 (n=30) was treated with Tropicamide and Flurbiprofen (0.03%). Two drops of drugs were instilled in each eye. Eye drops were placed within the conjunctival sac of the lower eyelid and patients were directed to close their eyes approximately for a minute after the instillation to prevent loss of medication via the punctum in the conjunctival sac. Before the instillation of first drop and at every ten minutes interval after the administration of eye drops up to one hour the pupil diameter was measured in all the groups. Two to three repeated measurements were taken within an interval of a few seconds at each time point and the mean value of the maximum horizontal and vertical diameter of the pupil was measured as pupil size. Data were expressed as mean $\pm$ SEM and subjected for ANOVA followed by Bonferroni post test by using Graphpad Prism Version 5.01(Graph Pad Software Inc., San Diego, USA).

## RESULTS

**Of the One-fifty Patients Enrolled Male:** female ratio is 97:53. The mean age of the patients and duration of

Table 1: Mydriatic effect of Tropicamide with Phenylephrine, Flurbiprofen in diabetic Patients

Group	Drug treatment(s)	Pupil dilation in mm
1	Tropicamide	5.4 $\pm$ 0.25
2	Tropicamide + Phenylephrine	5.9 $\pm$ 0.14
3	Tropicamide + Flurbiprofen	6.6 $\pm$ 0.47**

Pupil dilation is expressed as mean $\pm$ SEM, n-50 in each group; \*\* $P$ <0.01 as compared to Group

diabetes were 38.1 $\pm$ 9.6 years and 21.4 $\pm$ 8.1 years respectively. The mean HbA<sub>1c</sub> at the time of screening was 7.4 $\pm$ 0.6 percent.

Thirty two patients (21%) were already diagnosed as diabetic retinopathic and twelve patients (8%) had diabetic nephropathy and sixteen patients (11%) had diabetic neuropathy. Sixty eight patients (45%) were newly screened for their diabetic retinopathy progress and twenty two patients (15%) were diabetic with other co-morbid conditions.

The maximum pupil size in group 1 was 5.4 $\pm$ 0.25 mm and 5.9 $\pm$ 0.14 mm in group 2. Though there is a better dilation of pupil in group 2 when compared with group 1, it is statistically on-significant. Our interest of combination in group 3 brought out a pupil dilation of 6.6 $\pm$ 0.47 mm which is statistically significant ( $P$ <0.01).

## DISCUSSION

Treatment for diabetic retinopathy is preferred at early stages and involves laser treatment, intraocular steroidal injection and retinal repair depending on the progression of the disease [8, 9]. Ophthalmic screening in diabetic patients is very crucial and beneficial for prevention or early detection and effective treatment of diabetic retinopathy. The routinely used mydriatic drugs are in the combination of parasympatholytic with sympathomimetics as the regulation of the latter is being dominated by the former one. The combination therapy is preferred rather than mono therapy for producing the maximal dilation [10, 11].

The present study was undertaken to find out the effect of combination of drugs acting on different mechanism of action. Tropicamide blocks the acetylcholine action leading to the paralysis of cholinergically innervated sphincter iris muscles. As a result the adrenergic innervations to the radial muscle are unopposed and therefore leading to dilatation [12]. Phenylephrine, a sympathomimetic produces dilation of the pupil by potentiating the adrenergic action [13]. Flurbiprofen, a non-steroidal and anti-inflammatory drug is used to produce dilation of the pupil via inhibition of

cyclooxygenase enzyme. Cytokines such as TNF- $\alpha$  level are increased in diabetic retina due to leukocyte adhesion and breakdown of blood retinal barrier. Non-steroidal and anti-inflammatory drugs like Flurbiprofen, can suppress the TNF- $\alpha$  production eventually leading to reduction of leukocyte adhesion and finally developing a good retinal field [14, 15].

Apart from their mechanism of action, another important factor that requires prime attention is the proper time interval between the instillation of the eye drops. An immediate or late administration is not preferable as it may lead to the dilution of the mydriatic allowing it to remain intact in the conjunctival sac. Taking this into consideration a time interval of three minutes was given for the present study based on literature survey [6, 8, 11] and suggestion from ophthalmologist.

### CONCLUSION

The finding of the present study states that the combination of Tropicamide and Flurbiprofen can bring maximal pupil dilation among diabetic patients and can be practiced widely in ophthalmological and surgical screening process. The study can be further preceded by combining other drugs in right proportion.

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*Conflict of interest:* None.

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