

Improving Tolerance and Effectiveness of Cyclopentolate with Hydroxypropylmethylcellulose in Pediatric Population

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ABSTRACT

Purpose: The purpose of this study was to study the tolerance and effectiveness of cyclopentolate by combining with hydroxypropylmethylcellulose (HPMC) in children undergoing cycloplegic refraction. **Methods:** A total of 50 children attending pediatric ophthalmology outpatient department were recruited. The study regimen was a freshly prepared 1:1 combination of commercially available cyclopentolate (1%) with 2% HPMC. The control regimen was commercially available aqueous preparation containing cyclopentolate 1%. Each subject received both regimens of drugs, study regimen in one eye and control regimen in the fellow eye, with the eyes randomized to the drug regimen received. A single drop of the regimen was applied twice, at 0–5 min to one eye. The faces pain scale-revised score was recorded on instillation of the drops in each eye. Post-dilated retinoscopy, amplitude of accommodation (AA), and pupil size recorded in each eye at the end of 30 min. **Results:** Mean age was 11.3 ± 3.2 years (range 6–18 years). The most frequently recorded observation in the pain scale for the control regimen was 6, whereas for study regimen was 3. Mean pupil size was 4.68 mm for the study regimen and 4.56 mm for control regimen at the end of 30 min. Cyclopentolate with HPMC produced comparable reduction in AA ($2.2D \pm 1.16$) compared to plain cyclopentolate ($2.1D \pm 1.17$). Post-dilated retinoscopy values between the study and control regimen did not show any statistically significant difference ($P = 0.8$). **Conclusion:** Using HPMC, as a vehicle for cyclopentolate eye drops improves tolerance among children and maintains effectiveness.

Key words: Cyclopentolate, cycloplegic refraction, hydroxypropylmethylcellulose

INTRODUCTION

Cycloplegic refraction is necessary in children because of their high amplitude of accommodation (AA) and inability to give reliable subjective responses.^[1] Cyclopentolate is drug of choice for cycloplegia in children. Children fear instillation of these drops as it causes stinging and burning.^[2]

Since there is no effective replacement for cyclopentolate, minimizing its dosage without compromising its efficacy

would be ideal. Hydroxypropylmethylcellulose (HPMC) has been used as vehicle in many ophthalmic formulations to increase the efficacy.^[3] In an effort to create a child-friendly cycloplegia, we looked to compare tolerance and effectiveness of cyclopentolate in children with the addition of 2% HPMC.

MATERIALS AND METHODS

This was an interventional pilot study approved by the hospital ethics committee, and an informed consent was

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recorded from the parents of the children. 50 children in the age group of 6–18 years with the refractive errors from $0 \pm 0.25D$ (as confirmed by prior cycloplegic refraction, a month before the study) in both eyes were recruited from our pediatric outpatient clinic for participation in the study.

Children were excluded if they had anterior segment disorders severe enough to interfere with retinoscopy (e.g., corneal scar or lens opacity), a history of corneal or cataract surgery, accommodation problems, glaucoma, retinal problems, or known allergies to the cyclopentolate drops.

The study regimen was freshly prepared by 1:1 combination of commercially available cyclopentolate (1%) (Pentolate - Sunways, Mumbai) with 2% hydroxypropylmethylcellulose (Aurovisc) prepared under laminar flow hood with complete aseptic precautions. Once prepared the study regimen drops were used within 12 h. Commercially available aqueous preparation containing cyclopentolate 1% was taken as control regimen. Both the HPMC drops and the standard cyclopentolate kept at the same temperature before installation.

Each subject received both regimens of drugs, study regimen in one eye and control regimen in the fellow eye, with the eyes randomized to the drug regimen received. A single drop of the control or study regimen was applied twice, at 0 min–5 min to each eye. A 10 min interval was maintained between the applications of drop in either eye. Bottles used to deliver the HPMC drops and the cyclopentolate drops were identical and masked such that the observer rating the pain scale was unable to determine which drug was given to each eye.

The drops were instilled by one author who was not involved in data collection or analysis. All subsequent study measurements were conducted by an examiner who was masked as to which eye received each drug combination.

The faces pain scale-revised (FPS-R)^[4] score which is the measure of pain intensity, was recorded on instillation of the study and control regimen in each eye by another coauthor, who was also blinded for the nature of the drops.

The AA was measured at 30 min using Donders push-up method with the child wearing his/her best spectacle correction. Determinations were made monocularly and all measurements were repeated 3 times. The average was recorded. In addition, pupil size was recorded at the end of 30 min using pupil gauge in each eye. Post-cycloplegic retinoscopy was also done at the end of 30 min.

For analysis, AA, pupil size, and retinoscopy at 30 min after instillation of the second drop were used. Refractive errors were described using spherical equivalents.

The study ophthalmologist examined the anterior and posterior segment with a slit lamp and by indirect ophthalmoscopy. Self-reported symptoms and side effects were noted.

Data were analyzed descriptively initially. The mean and standard deviation were calculated. Independent sampled *t*-test was used to compare the mean difference between study and control eyes. A two-sided $P < 0.05$ was considered to be statistically significant. Analysis was carried out using the SPSS version 17.0 (SPSS, Chicago, IL, USA) for windows.

RESULTS

Mean age was 11.3 ± 3.2 (range 6–18 years). There was no statistically significant difference in the mean spherical equivalent values for both eyes using the two drug regimens.

The mean AA of study regimen at the end of 30 min was 2.2 ± 1.16 Diopters and control regimen was 2.1 ± 1.17 D, and this difference was not statistically significant ($P = 1.000$) [Figure 1].

The most frequently recorded observation in the FPS-R score for the control regimen was 6, whereas for the study regimen was 3 [Figure 2]. Furthermore, considering a score of 0–4 as tolerant, tolerability was 88% in the study group as against 24% in the control group.

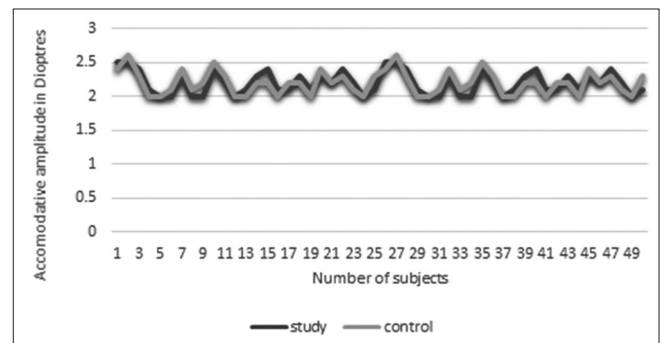


Figure 1: The line graph depicting the amplitude of accommodation values obtained by study and control regimens

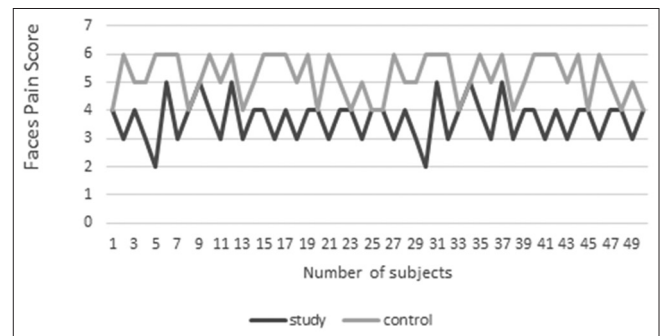


Figure 2: The graph demonstrates the faces pain scale score with study and control regimen

The mean pupil size at the end of 30 min was 4.68 ± 0.28 mm for the study regimen and 4.56 ± 0.26 mm for control regimen [Figure 3], and this difference was statistically significant ($P = 0.029$) showing slightly better pupillary dilation with the study regimen. Post-dilated retinoscopy values between the study and control regimen did not show any statistically significant difference ($P = 0.8$).

There were no adverse events in the study population with either drug.

DISCUSSION

Cycloplegic refraction has been described as an essential part of the pediatric ophthalmic assessment and the cornerstone of strabismus evaluation.^[5] Cyclopentolate is the commonly used cycloplegic agent in pediatric refraction. Children commonly complain of stinging and burning sensation on installation of cyclopentolate eye drops. This subsequently makes the child non-compliant to further examination as well.

Many modalities of using a sprayer with cyclopentolate and addition of proparacaine have been tested to reduce the stinging and also increase the duration of action of the drug.^[6,7] However, the unavailability of a commercial spray to dispense the drop and the decrease in the dosage due to the blink response does not allow widespread use of a sprayer. The inherent stinging due to paracaine negates any benefit to the child from combining the same with cyclopentolate.

Ocular drug delivery has remained as one of the most challenging tasks for pharmaceutical scientists. The unique structure of the eye restricts the entry of drug molecules at the required site of action. Most of the topically applied drugs are washed off from the eye by various mechanisms (lacrimal drainage, tear dilution and tear turnover), resulting in low ocular bioavailability of the drugs. As a result of these factors, <5% of the administered drug enters the eye.^[8] One of the main reasons for that is the poor residence time of the drug at the site of action, which results in poor bioavailability.

Ocular bioavailability of several drugs has been increased by administering them in viscous polymeric solutions.^[9] Carboxymethyl cellulose and HPMC have film-forming properties and HPMC is specifically able to interact with the tear film increasing its stability. Viscosity enhancing of drug solutions poses many advantages such as improving consuming controllability and increasing residence time of drugs in topical and mucosal solutions, which helps in improving the bioavailability of topical, nasal, or ocular preparations.^[10]

The increased ocular bioavailability of the drug in our study was due to the longer corneal contact of the viscous solution,

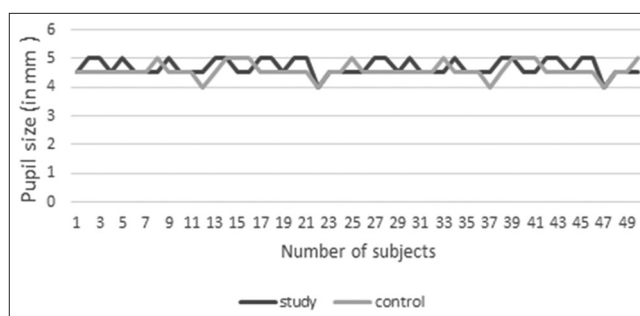


Figure 3: This graph depicts the pupil size at the end of 30 min with the study and control regimens

and the reduced systemic drug load may have been caused by the slower spreading of the solution on the nasal mucosa.^[11]

The tolerability of the drug increased significantly in majority of the children with addition of HPMC to the active drug.

The use of HPMC could find a role in other mydriatics and ocular drugs used in the outpatient clinic to increase their tolerance. Here, we have used a higher viscosity drug (HPMC 2%) and not noted any significant reduction in the cycloplegic effect.

The use of FPS-R is a subjective measure of the tolerability. We may need to further study the polymer concentration to optimize the efficacy of the drug with maximum tolerance to enhance the comfort of the drug when applied. We did not undertake a chemical analysis to see if either of the drugs were altered after mixing as it was not the objective of this study.

The limitations of the study being the smaller sample size and the subjects were children aged 6–18 years. The diluted concentration of cyclopentolate after the drug was mixed with HPMC was not assessed. If younger children were included in the study, the results may have been more reliable because they have a higher AA. As this formulation is better tolerated, this could translate into better cooperation with younger kids.

CONCLUSION

Addition of HPMC to cyclopentolate was clinically equivalent to cyclopentolate for achieving effective pupil dilation and cycloplegia. Using HPMC as a vehicle for cyclopentolate, eye drops improve tolerance among children and maintains effectiveness. This could have a bearing on the compliance to regular cycloplegic examinations that are required in children.

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