Cycloplegic Efficacy of Cyclopentolate Ointment Vs. Cyclopentolate Solution

by

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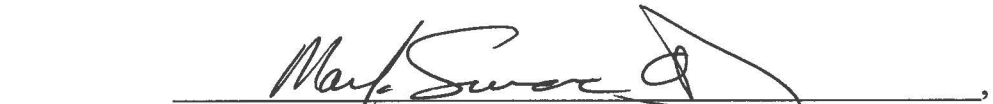
APPROVED:



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Introduction:

Cycloplegic examinations are the standard of care for children. They are used to determine the full amount of prescription a child has, without the concern for their high accommodative capabilities to result in under-corrected refractive error. Baseline refractive error is important in preventing and treating amblyopia and other binocular deficits. Eye drops have been the historical modality of instilling cycloplegics, but these cause considerable discomfort for children which can disrupt the exam and create an unwilling patient. Ophthalmic ointments have been found to be more comfortable upon instillation than equivalent ophthalmic drops (Cable). Cyclopentolate hydrochloride is considered to be the medication of choice for determining cycloplegic refractive error but is only available from pharmaceutical distributors in solution form (Manny). This study will investigate if the compounded ointment form has an equivalent cycloplegic effect when compared to the solution form, as measured by autorefraction, and whether the added cost of obtaining the medication in ointment form is justified by improved patient comfort and facility of the exam. The ointment form would offer better patient cooperation and less disruption to examinations. This would help in sensitive patients or children who respond so negatively to the stinging of drops, as well as in the disabled or patients who are unable to lift their head for drops. Due to the irritating nature of preservatives, increased lacrimation washes out some of the drug, yielding a decreased amount of drug penetrating the cornea (Ismail). Drops generally are not well retained in the eye, but are squeezed or drained out through the nasolacrimal duct (Goodman). It has been reported that ointments are equally, or more, effective than topical drops in solution or liquid suspension form, and they cause less irritation and require less amounts of the

drug (Cable). The side effects of drugs in ointment are the same as equivalent drugs in drop form because ointments have the same systemic absorption (Fiscella, Scruggs).

Methods:

The Human Subjects Review Committee at Ferris State University approved this study. After recruiting volunteers to participate in the study, specific dates and times were made available to sign up for the study. If a volunteer was felt to be a good candidate for the study, the patient was informed of all aspects of the study and asked to participate. All subjects read and signed the consent form provided. Subjects ranged in age from 21 to 29, three males and six females, and varying irides from light blue to brown.

Preliminary data were collected to determine if the subject was a suitable candidate to participate in the study. All of these criteria were typical visual attributes commonly assessed in a standard eye examination using established protocols. Subjects must have met the following criteria: Von Herrick angles greater than one (1), corrected distance visual acuities of 20/30 or better (OD and OS), cover test at both distance and near to rule out strabismus and clinically significant AC/A ratio (<2/1 or >6/1), normal lag of accommodation, and an initial distance autorefractor reading to verify the subject has 2.0 diopters or less of astigmatism. Subjects who met all of the inclusion criteria were randomized into two treatment groups.

Readings were all taken with myopes wearing spherical contact lens prescriptions that were appropriate for their spherical equivalent error and removed during the 30 minutes

between drug instillation and final readings. Autorefractor readings were all taken with the Grand Seiko WR-5100K Autorefractor. A reported advantage of the Grand Seiko WR-5100K Autorefractor is that patients view the actual environment through a window. This window does not create an artificial environment and therefore yields more accurate errors. The instrument also allows for non-artificial measurements with the patient viewing targets at any distance the examiner chooses, making it optimal for near refractive readings.

Ten preliminary distance autorefractor measurements were taken in primary gaze for the right and left eyes separately, converted to spherical equivalent and averaged for each patient. Then ten preliminary near, 2.5 D accommodative demand, autorefractor readings were taken in primary gaze for the right and left eyes, at 40 cm with a near snellen acuity chart for an accommodative target. Based on the pre-arranged randomized assignment, one eye was to be treated with anesthetic and cycloplegic solution (drops) and the other eye cyclopentolate ointment. The anticholinergic agent, cyclopentolate hydrochloride, was the pharmaceutical being tested. The standard form is a 1% cyclopentolate solution. An ointment compounded directly from the 1% cyclopentolate solution was the subject of comparison. The ointment was compounded at Diplomat Pharmacy, Flint, Michigan from 1% cyclopentolate solution and bland ophthalmic ointment. The solution procedure involved placing 1 drop of 0.5% proparacaine HCl (anesthetic agent) into the inferior cul-de-sac of the eye according to standard clinical protocol, followed by 1 drop of 1.0% cyclopentolate HCl solution (cycloplegic agent), 30 seconds later. The ointment procedure involved placing approximately a 3mm round dollop of 1.0% cyclopentolate

HCl ointment onto a sterilized scleral depressor (external ophthalmic probe) then placing the ointment into the inferior cul-de-sac.

After allowing thirty minutes for subjects to achieve full cycloplegia, the spherical equivalent average of ten distance measurements were taken in primary gaze for each eye. Finally, the spherical equivalent average of ten near readings, 2.5 D accommodative demand, were taken for both the right and left eyes. All measurements were recorded separately from the subject's agreement sheet, at which time it was converted to spherical equivalent and averaged. The data recorded were analyzed in the following manner. Near measurements were compared to distance measurements, from the WR-5100K. Comparisons were made between pre-drug near and distance, cyclopentolate ointment treated eyes near and distance, and cyclopentolate solution treated eyes near and distance. Finally, cyclopentolate ointment treated eyes were compared to the results of the cyclopentolate solution treated eyes in order to determine the effectiveness of the ointment.

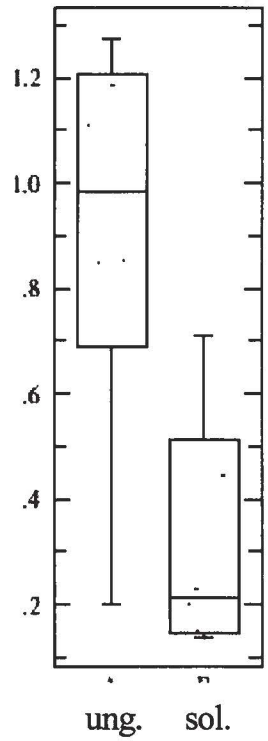
Results:

The information from 12 of 18 eyes, 6 of 9 people, was used. The average pre-drug accommodation for the 12 eyes was 1.54 diopters. Two eyes were excluded for astigmatism greater than 2 D, giving inconsistent pre-drug/post-drug refractive errors, and four eyes due to errors with

	ointment	solution	difference
Pt 1	0.2	0.14	0.06
Pt 3	1.11	0.2	0.91
Pt 4	1.185	0.71	0.475
Pt 6	1.275	0.445	1.45
Pt 7	0.85	0.23	0.62
Pt 8	0.855	0.15	0.705

diopters of remaining accommodation

subject's contact lenses giving results of more accommodation post-cycloplegia than the accommodative demand itself. The remaining data showed that pre-drug and post-drug distance refractive error was repeatable. The ointment and solution, remaining accommodation, were then compared. The data obtained were statistically analyzed using a student's unpaired t-test to see if the two sets of data are really different. The table shows the average amount of remaining accommodation as a positive number, in diopters, for each subject, giving a side-by-side comparison for the ointment and solution. The higher the number equals more remaining accommodative ability or less cycloplegic effect. The last column shows the difference between the results for each subject. The graph shows the range of each modality, along with the average and outliers. It is clear to see from this table and graph that the solution was more effective in causing cycloplegia, reduced accommodative ability. The mean accommodation using cyclopentolate solution with proparacaine was 0.313 D with a standard deviation of 0.224 D. The measurements ranged from 0.14-0.71 D. The mean accommodation using cyclopentolate ointment alone was 0.913 D with a standard deviation of 0.390 D. The measurements ranged from 0.20-1.27 D. By comparing the results based on mean accommodation and standard deviation alone, there does appear to be some correlation between the two methods of cycloplegia. In fact, the t-test showed a p value of 0.0084 and a correlation coefficient of 0.622. The average difference between the measurements of all readings was 0.703 D.



Discussion:

The results do not show that the cyclopentolate ointment worked equally or better than that of the cyclopentolate solution when used with proparacaine. The data suggest that there is some correlation between the accommodation measurements taken with the cyclopentolate ointment and the standard cyclopentolate solution. This conclusion is supported with the results of a correlation coefficient of 0.622, though the unpaired t-test that provided a p value of 0.0084 suggests these results are not likely to occur in future trials. The ointment was reported to cause initial blurring of vision and the instillation took longer than was desired and expected. All nine subjects did report that the cyclopentolate ointment alone was more comfortable than the drop of proparacaine instilled prior to cyclopentolate solution.

This study was intentionally weighted/flawed against its success. This was achieved by only using proparacaine in the eye receiving cyclopentolate solution. Proparacaine has been shown to loosen corneal epithelium and allow for better penetration of follow-up drugs, cyclopentolate solution in this study (Lesher). The eye receiving cyclopentolate ointment did not have this advantage, in hopes that it would be shown to be equally or more effective than the effects of the solution with proparacaine.

Difficulties with this study that may have had an impact were the following. The ointment would have been preferable if it had a lower melting temperature. The room temperature ointment, scleral depressor and cool retracted lower eyelid made it difficult

for the ointment to easily melt off into the cul-de-sac of the lower lid and took about 30 seconds to deposit with varying amounts deposited. Another problem may have been that 30 minutes may not have been enough time to cause sufficient cycloplegia, due to increased melting time (dispensing of drug to ocular surface), in a sense creating an offset, delayed initiation time for the eye receiving cyclopentolate ointment. This may have been compounded if we had a high number of dark irides, according to a time course study. The time course study suggests that only 10 minutes is needed for light irides but that 30 to 40 minutes is required for dark irides (Manny). Though this alone does not explain the difference of cycloplegia variation between the ointment and solution.

In a previous study, it was determined that a 2% cyclopentolate concentration of ointment was needed to produce cycloplegia equivalent to 1% cyclopentolate drops (Cable). That study compounded the ointment from evaporated cyclopentolate solution crystals reconstituted, as opposed to the method used in this study: direct compounding of 1% cyclopentolate solution into bland ointment. The 2% cyclopentolate may be necessary for equivalent cycloplegic effect in this simplified compounding method too. It should also be pointed out that this test of cycloplegic effect was more robust than many other studies in that subjects were given an actual near target and encouraged them to try to clear it, which is different than determining the change in distance refractive error.

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