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A COMPARISON BETWEEN ATROPINE AND CYCLOPENTOLATE IN CYCLOPLEGIC REFRACTION IN CHILDREN

Divashini Kisten

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine.

Johannesburg, 31 July 2019

DECLARATION

I, Divashini Kisten, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Signature

31st day of July 2019 in Sandton

CONTRIBUTION OF STUDENT TO SUBMISSIBLE ARTICLE

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Divashini Kisten, student number 0501023M, declare that this Research Report is my own work and that I contributed adequately towards research findings presented in the paper intended for publication below.

Signature of Student.....**Date** 12/05/2019

Name of Primary Supervisor: Prof I Mayet

Signature of Primary Supervisor.....**Date** 13/5/2019

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of his/her Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article Title: A Comparison Between Atropine and Cyclopentolate in Cycloplegic Refraction in Children

Authors	Name	Signature	Date
1st author	Divashini Kisten		12/05/2019
2nd author	Prof I Mayet		13/5/2019

Comments by primary supervisor:

_____

_____

_____

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SUBMISSIBLE ARTICLE

Abstract

Background: Cycloplegic refraction is a reliable procedure for obtaining an accurate refraction in children. Atropine is considered the gold standard, however, it does not have the properties of an ideal cycloplegic agent. Theoretically, cyclopentolate is the preferred agent and many have advocated it as an alternative. In the African population where dark irides are common there is insufficient information comparing the two agents, especially so in younger aged children.

Objective: To establish if cyclopentolate is as effective as atropine in cycloplegic refraction in dark irides**.**

Method: A prospective, sequential, paired study on patients requiring cycloplegic refraction was conducted. Each patient was refracted after the usage of cyclopentolate. Refraction was then repeated 2 weeks later after using atropine.

Results: 40 patients (80 eyes) were refracted with both agents. The mean difference between the agents (atropine – cyclopentolate) was +0,14 DS (95% CI: +0.05 to +0.24; paired t-test; p=0.0027), however, the effect size was small (Cohen's d=0.35) making it clinically insignificant. No adverse effects were reported with either of the cycloplegic agents.

Conclusion: Cyclopentolate is as effective as atropine for cycloplegic refraction in dark irides and can be used as an alternative to atropine for cycloplegic refraction.

Introduction

Refraction is an integral part of the ophthalmic assessment in all patients. Obtaining accurate refraction relies on the relaxation of accommodation by asking a patient to fixate on a distant target. This is not always possible in children and cycloplegia (relaxation of accommodation using drugs) becomes essential for refraction. Therefore cycloplegic refraction remains a reliable and valid procedure for obtaining an accurate refraction, especially so in young children as it does not depend on patient cooperation or fixation distance.[1,2]

The refracting power of the eye is the result of a combination of its static and accommodative power. Static power is the ability of the cornea and lens to bend incoming rays of light. It is the power of the eye at rest. Accommodative power, in contrast, is a variable force that alters the path of light rays using the ciliary body to

change the curvature of the lens, thereby adjusting the focus of the eye. There is, however, a maximal increase in the optical power that an eye can achieve by adjusting its focus. The difference of power between the eye at rest (static power) and the fully accommodated eye (maximum accommodative power) is known as the amplitude of accommodation.[1,3]

The accommodative power of the eye can be inhibited by blocking the action of the ciliary body by using cycloplegic drugs.[1,3,4] Five such drugs are available for topical use in the eye: atropine, scopolamine, homatropine, cyclopentolate and tropicamide (in order of decreasing strength).[4,5] Cycloplegic agents should be used with caution in infants as they have immature metabolic and excretion systems, which make them more vulnerable to systemic complications. All cycloplegic agents result in mydriasis and loss of accommodation from several hours up to several days, depending on the type of agent used.[1,4] The amount of iris pigmentation affects the efficacy of all of these agents, with dark irides possibly needing longer times to maximal cycloplegia.[4] The cycloplegic drugs which are most routinely used are atropine and cyclopentolate.[5]

Atropine has both mydriatic (pupillary dilatation) and cycloplegic (accommodative inhibition) properties; and is the most potent agent available. Typically a 1% solution is administered as a single drop twice a day for 1-3 days.[1,5] Using this dosing protocol, 3 days are required to produce complete cycloplegia. The cycloplegic effect lasts between 7-12 days.[2,4-6] Ocular side effects are rare and most commonly include direct irritation and stinging on instillation. Dose-dependent systemic effects can occur due to absorption from the conjunctival vessels and the nasal mucosa. The most common systemic side effects are fever, restlessness and hallucinations. Certain people appear to be more susceptible to side effects including infants, the elderly, lightly pigmented individuals, and individuals with spastic paralysis, Down syndrome or other central nervous system (CNS) disorders.[4]

Cyclopentolate also has both mydriatic and cycloplegic properties. It is administered 30-45 minutes before the examination as 2-3 drops given 5-10 minutes apart.[4-6] Maximal cycloplegia is reached at 20-45 minutes and usually lasts 6-24 hours when using a 1% solution.[2,4,5] It is the cycloplegic with the fastest onset and shortest recovery time, and it is the only cycloplegic where the maximum onset of cycloplegia approximates the maximum onset of mydriasis. This allows the use of the fully dilated pupil to indicate full cycloplegia. Similarly with atropine, the most common ocular side effect is stinging on instillation and the systemic effects are dose-dependent. The

central nervous system is the most affected and cyclopentolate may result in visual and tactile hallucinations. Adverse effects are again more likely to occur when using higher concentrations in infants, the elderly, individuals who have neurological impairment, spastic paralysis or other CNS disorders.[4-6]

An effective cycloplegic agent is essential to cycloplegic refraction. The ideal cycloplegic agent should have a rapid onset with adequate duration of maximum cycloplegia, complete paralysis of accommodation, rapid recovery of accommodation and an absence of side effects.[2] No cycloplegic agent possesses all of these properties and there is no agreement as to which agent is ideal. Atropine is however the gold standard for complete cycloplegia, but it has a difficult administration regimen. It requires a second consultation with instillation 3 days prior to the examination and the effects last between 7-10 days. It requires administration at the patient's residence. This makes compliance an additional factor to consider. It also has more side effects and longer impairment of near vision than cyclopentolate, which has been advocated as an alternative. The shorter acting cyclopentolate has the advantage that the cycloplegic refraction can be performed during the first consultation and the effects usually only last 24 hours.[2,6-8]

Several studies have compared the effect of cyclopentolate with atropine with regard to refraction, to determine if it could be used as a suitable alternative. However, the literature on this topic is limited and evidence from previously conducted studies are conflicting. Some have shown atropine to uncover more hyperopia than cyclopentolate, especially in younger children. Whereas others have found no overall difference. There has also been some suggestion that dark irides require a more potent cycloplegic agent. Previous studies were also limited by the age group of the children who were above the age of 3 years.

Cycloplegic refraction in children is routinely conducted at our institution, St John Eye Hospital (SJEH). Atropine is the cycloplegic agent that is prescribed for most children above the age of 1 year at SJEH, as it is the gold standard, despite it having the least desirable properties compared to an ideal cycloplegic agent. Cyclopentolate is the theoretically preferred agent and has been advocated as an alternative. There is evidence that cyclopentolate compares to atropine in efficacy in cycloplegic refraction. However, there is insufficient information available in the African population and especially so in younger children. It was on this background that a prospective study comparing the two agents in cycloplegic refraction in children was conducted.

Objectives

To determine if cyclopentolate is as effective as atropine for cycloplegic refraction in dark irides and to determine if cyclopentolate could be used as an alternative to atropine for cycloplegic refraction.

Materials & Method

This study was conducted at SJEH and was a prospective, sequential, paired design with each eye acting as its own control. Ethics approval was obtained from the Human Ethics Research Committee of the University of the Witwatersrand.

The sample size calculations were carried out in G*Power.[11] Comparing the refraction measured with the use of atropine with that obtained with the use of cyclopentolate required the use of a paired t-test. Assuming to find a medium size effect with 80% power at the 5% significance level, the sample size was calculated to be 80 eyes (40 patients).

Inclusion criteria into the study required children to be between 1 to 6 years of age, and to have dark irides. Patients with ophthalmic disease that would prevent performing refractive assessment and those that failed to follow up with study visits were excluded from the study. A total of 40 patients presenting to the paediatric ophthalmology clinic at SJEH for cycloplegic refraction who fulfilled the inclusion and exclusion criteria were enrolled.

All patients were assessed by the primary investigator prior to the instillation of cycloplegic agents. A detailed history was obtained and an ophthalmological examination was performed. Informed consent was obtained from the patients' parent or guardian.

On the first visit, each patient had 3 drops of 1% cyclopentolate instilled 5 minutes apart with refraction assessed after 45 minutes. Two weeks later, the same patient had 1% atropine instilled twice daily for 3 days before and on the day of refraction. One drop was administered into the lower fornix of the eye and digital pressure was applied for a few minutes to the lacrimal puncti. The parents or guardians of the patients who were administering atropine were explained in their language of choice by nursing staff on how to administer the drops.

The refractions were carried out by the primary investigator in a dark room using a retinoscope. All refractions were validated by one of the paediatric ophthalmic consultants who was blinded to the agent used. The obtained values were converted

into the spherical equivalent. Data was captured on a standardised data collection sheet and then transferred to an excel spreadsheet.

Data was analysed in conjunction with a statistician using STATISTICA v13.1. A descriptive analysis of the results and a comparison of the refraction between the two agents using the paired t-test was conducted. A 5% significance level was used.

Results

To acquire the required 40 patients, the study was conducted between February 2018 to January 2019.

The mean age of the patients was 4 years (IQR 3-5 years; range 1-6 years). *Figure 1* shows the distribution of age among the study patients.

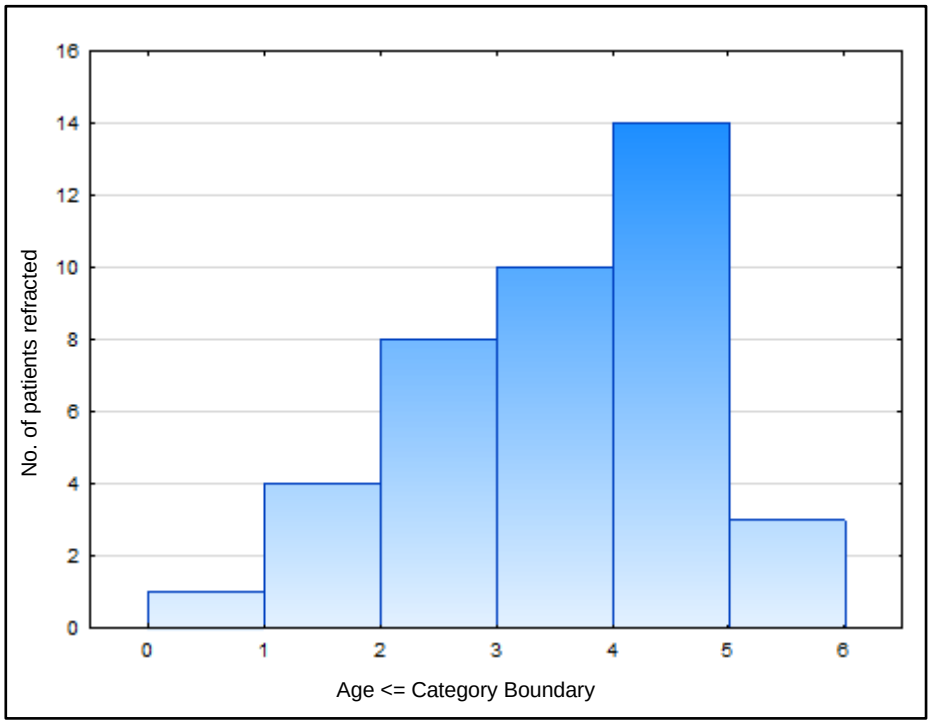

Figure 1: Distribution of age of study patients

53% of the patients in the study were female. Analysis of the medical history revealed that there were several ophthalmic conditions, these were obtained from patient medical records *(Figure 2).* Some patients had more than one diagnosis. The most common ophthalmic diagnoses amongst the study patients were strabismus (manifest and intermittent) (40%) and vernal keratoconjunctivitis (VKC) (40%).

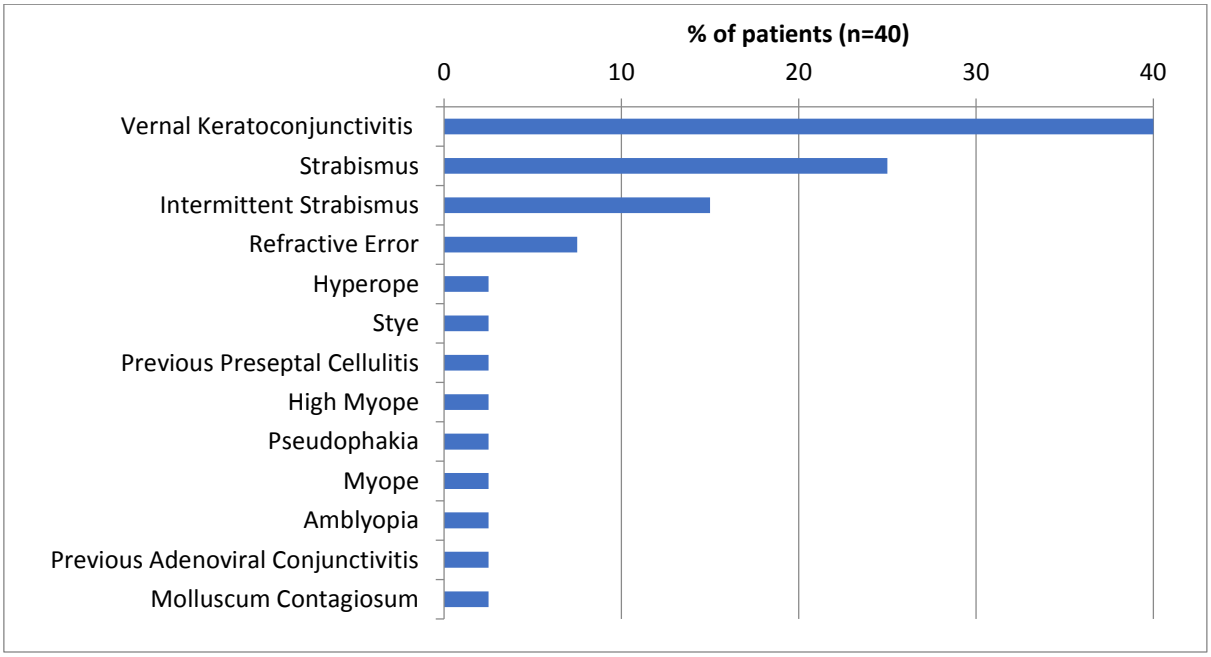

Figure 2: Ophthalmic conditions present in the study patients

58% of patients were not using any medication at the time of examination. *Figure 3* indicates the medication usage in the study patients. Some of the patients used more than one topical agent, therefore the percentages sum to more than 100%.

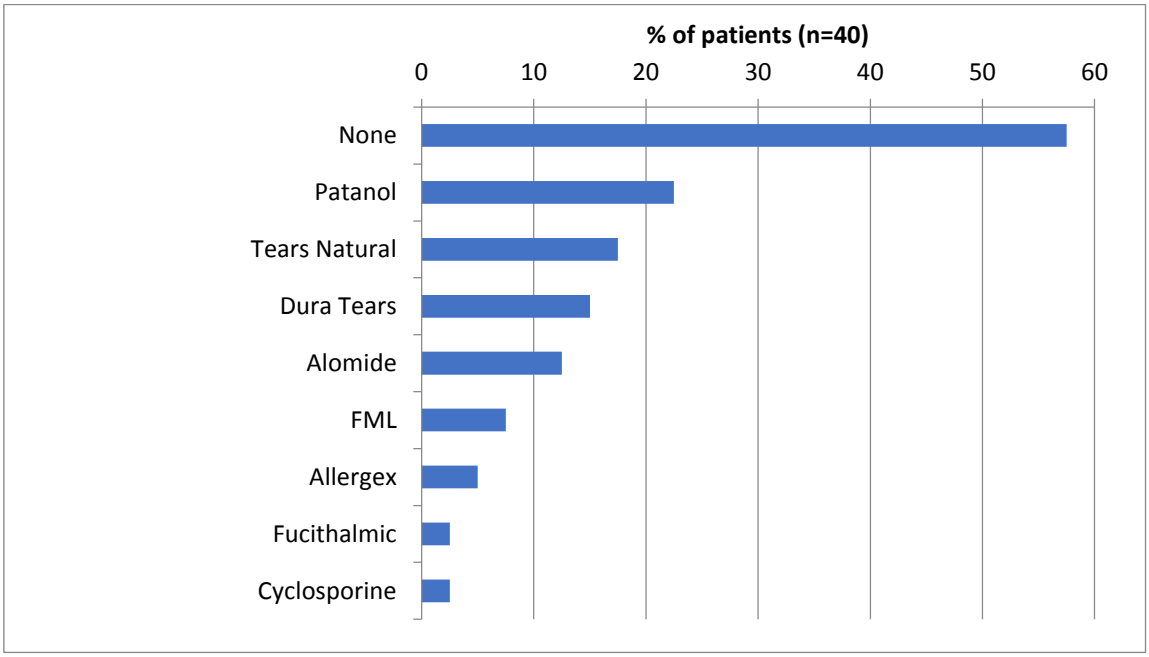

Figure 3: Medication usage in the study patients

No patients in the study reported any known allergies. The pre-instillation assessment revealed 58% of patients to have a normal examination, whilst 20% had an alternating esotropia (*Figure 4*). The clinical findings at the preinstallation

examination did not fully correlate with the medical history, which was taken from medical records. This was especially so for strabismus, where 40% of the patients required cycloplegic refraction for strabismus but on examination only 20% were noted to have this condition.

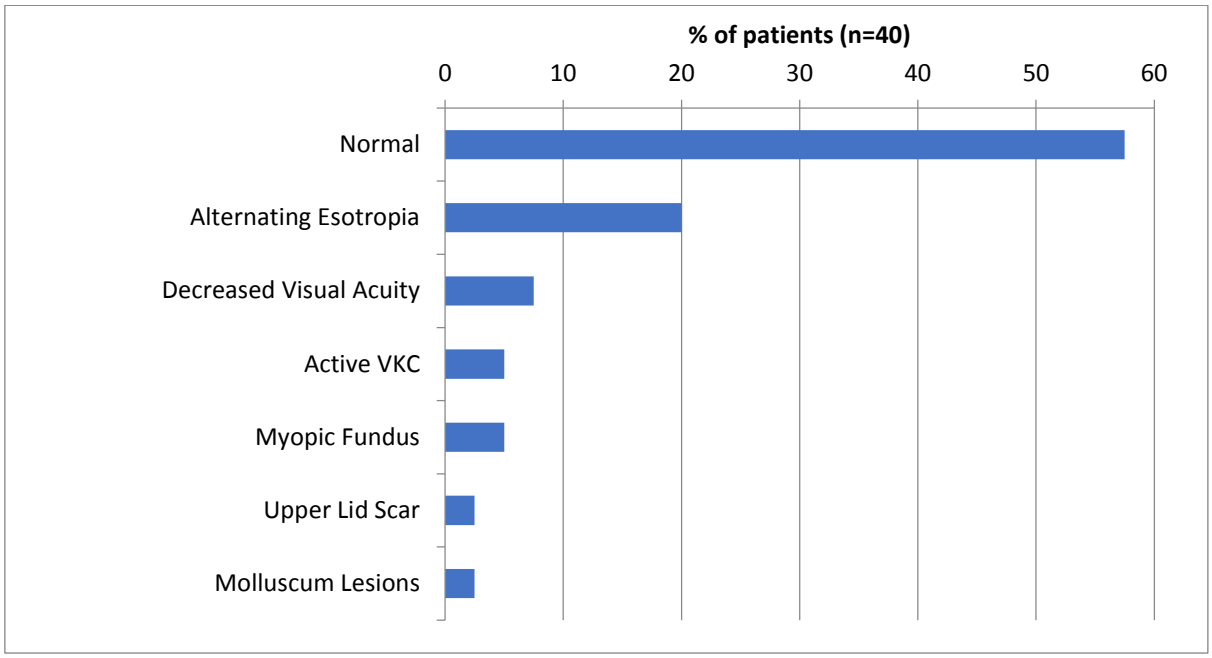

Figure 4: Pre-instillation findings in the study patients

The mean refraction with cyclopentolate was +1,90 diopter sphere (DS) (SD 3.7; range -16.00 to +10.50) and with atropine being the cycloplegic agent was +2,10 DS (SD 4.0; range -17.00 to +10.50). *Figures 5 and 6* show the distribution of data for cyclopentolate and atropine, respectively.

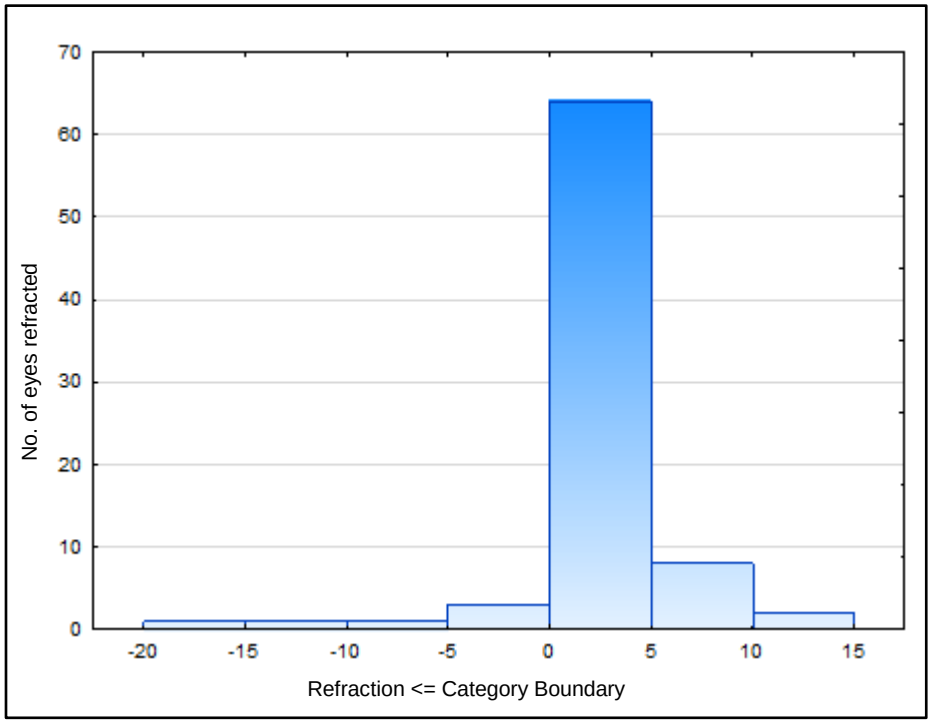

Figure 5: Distribution of data for cycloplegic refraction with cyclopentolate

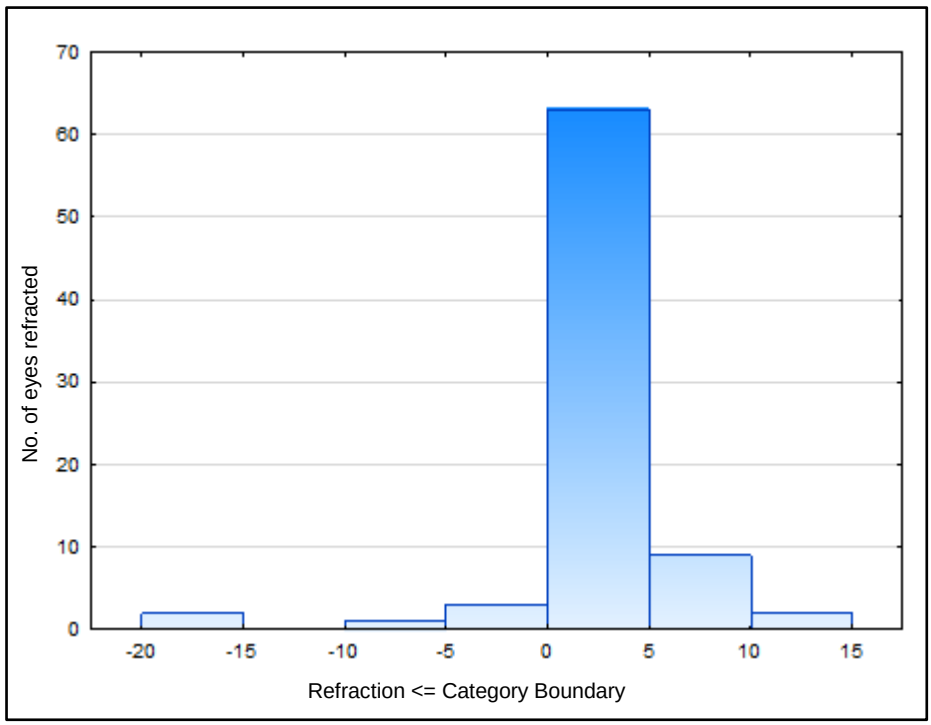

Figure 6: Distribution of data for cycloplegic refraction with atropine

The mean difference in refraction (atropine – cyclopentolate) was +0,14 DS (95% CI: +0.05 to +0.24). The paired t-test showed a statistically significant difference between the two agents (p=0.0027) (*Figure 7*) ,however, the effect size was small (Cohen's d=0.35).

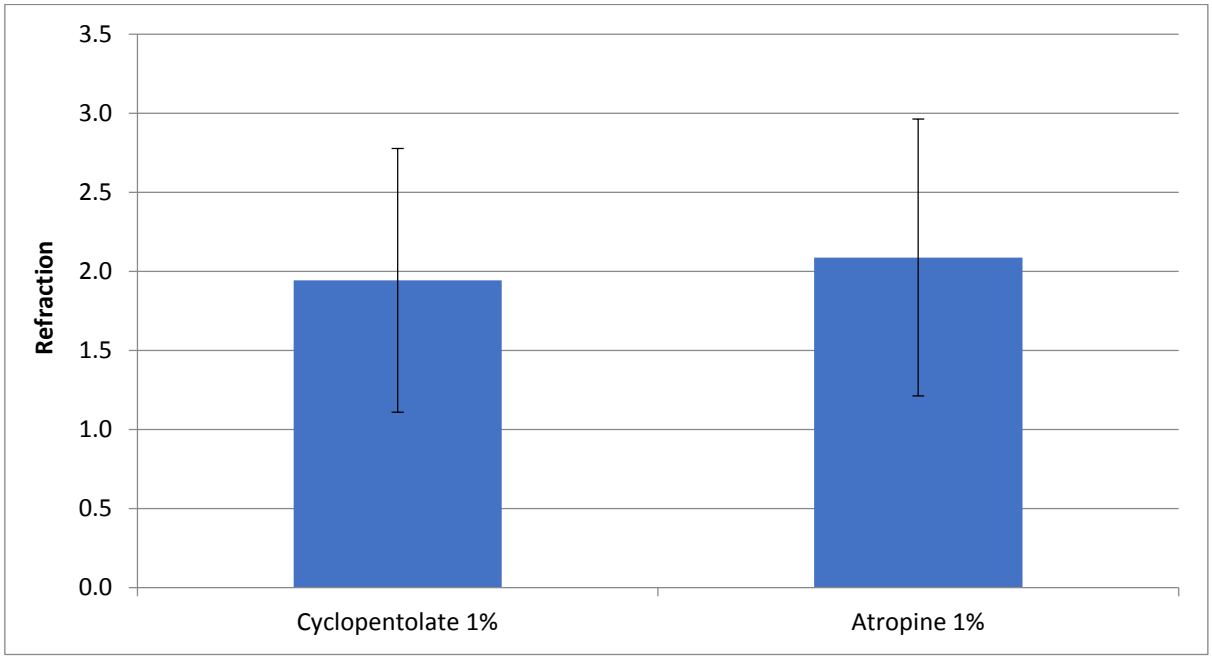

Figure 7: The mean difference in refraction between cyclopentolate and atropine

There were no adverse effects reported in the study group with either of the cycloplegic agents.

Discussion

Atropine and cyclopentolate have been compared with regard to cycloplegic refraction in several studies to determine if cyclopentolate could be a suitable alternative to atropine. However, the literature is limited and certain aspects are conflicting.

Our study shows no clinical difference albeit a statistical difference (+0,14 DS) between the refraction with atropine and cyclopentolate. This indicates that the cycloplegic agent cyclopentolate is an adequate alternative to atropine in dark irides. The findings in our study differed from the findings of Ingram and Barr[9] who conducted one of the first studies, which reported more hyperopia with atropine in 1 year old children. A more recent study (Farhood, 2012)[8], noted no overall difference with the 2 agents, but also noted children younger than 5 years of age to have more hyperopia uncovered with atropine. These results were compared to the findings of Robb and Peterson which showed a similar finding in children younger than 6 years, but was in contrast to the findings of Rosenbaum who showed that atropine was probably unnecessary when studying Caucasian esotropic children younger than 5 years.[8] The patients in our study were all between the ages of 1 and 6 years. In this

younger group of patients who all had dark irides, there was no clinically significant overall difference noted, including hyperopia. An African study conducted in Nigeria (Ebri et al [10]) on older children (4-15 years) with dark irides reported a significantly lower mean residual accommodation with atropine. These findings differ to the findings of our study. Sani et al[7] also conducted an African study in Nigeria in which atropine was compared to a cyclopentolate-tropicamide combination. A similarity was noted in the refractions, however, the children in this study were limited to the age of 5-12 years. The children in both the studies in Nigeria were older than those in our study. Older children have a lower amplitude of accommodation and therefore are in less need of cycloplegia.

During the study it was noted that a number of patients did not follow up with the second appointment (refraction with atropine) and had to be excluded, therefore further patients were needed to meet the planned sample size. This highlights the issue of compliance. This emphasises the need for cycloplegic refraction to be performed on the first consultation. Atropine is unsuitable for this due to the time to maximal cycloplegia which is 3 days. Cyclopentolate is the more suitable drug to avoid non-compliance to consultations.

In contrast to the literature on side effects, none of our study patients reported any side effects with either of the agents. This was so even though atropine administration was performed by the caregiver at the patient's residence for 3 days before the refraction. The dose dependent systemic side effects are another important factor to consider when choosing a cycloplegic agent as cyclopentolate is administered by a health care worker in a health care facility as opposed to atropine being administered by a caregiver outside of healthcare supervision, which may result in accidental over dosing in the patients' residence.

A possible limitation in the present study is that the primary investigator was not blinded to the agent being used for the refraction. However, the consultant who verified the refraction was blinded.

A recommendation for further studies would be to have a blinded person performing the refractions.

Conclusion

This study found that 1% Cyclopentolate is as effective as atropine for cycloplegic refraction in dark irides and can be used as an alternative to atropine for cycloplegic refraction.

Acknowledgements

The nursing staff at SJEH for assisting with patient education and information; the consultants of the paediatric clinic who validated the refractions.

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APPENDICES

Appendix A: Approved protocol

RESEARCH PROTOCOL

A Comparison Between Atropine and Cyclopentolate in Cycloplegic Refraction in Children

Dr Divashini Kisten

Registrar

MMed Student

Student Number: 0501023M

Department of Neurosciences

Division: Ophthalmology

University of Witwatersrand

Supervisor:

Prof I Mayet

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1. Introduction & Literature Review

Introduction:

The refracting power of the eye is the result of a combination of its static and accommodative power. Static power is the ability of the cornea and lens to bend incoming rays of light. It is the power of the eye at rest. Accommodative power, in contrast, is a variable force that alters the path of light rays using the ciliary body to change the curvature of the lens, thereby adjusting the focus of the eye. There is, however, a maximal increase in the optical power that an eye can achieve by adjusting its focus. The difference of power between the eye at rest (static power) and the fully accommodated eye (maximum accommodative power) is known as the amplitude of accommodation.[1,2]

Refraction is an integral part of the ophthalmic assessment in all patients. Obtaining accurate refraction relies on the relaxation of accommodation by asking a patient to fixate on a distant target. This is not always possible in children and cycloplegia (relaxation of accommodation using drugs) becomes essential for refraction. Cycloplegic refraction therefore remains a reliable and valid procedure for obtaining an accurate refraction, especially so in young children as it does not depend on patient cooperation or fixation distance. It allows the diagnosis of refractive error in children with refractive or accommodative esotropia, pseudomyopia, latent hyperopia, anisometropia and amblyopia. It is also useful in determining refractive error in patients who are uncooperative with subjective refraction, unable to communicate, inconsistent or those in which a functional visual deficit is suspected.[1,3]

The accommodative power of the eye can be inhibited by blocking the action of the ciliary body. Cycloplegic drugs are used for this. They are parasympathetic muscarinic agents, which results in some degree of pupillary dilation and cycloplegia.[1,3,4] Five such drugs are available for topical use in the eye.[4] They are atropine, scopolamine, homatropine, cyclopentolate and tropicamide in order of decreasing strength.[4,5] Cycloplegic agents should be used with caution in infants as they have immature metabolism and excretion systems, which make them more vulnerable to systemic complications. All cycloplegic agents result in mydriasis and loss of accommodation from several hours up to several days depending on the type of agent used. This results in blurred near vision.[1,4] The amount of iris pigmentation affects the efficacy of all of these agents.[4]The drugs which are routinely used are atropine and cyclopentolate.[5]

Atropine is a naturally occurring alkaloid and is a nonselective muscarinic antagonist. It has both mydriatic (dilates the pupil) and cycloplegic properties and is the most

potent available agent. Using a 1% solution, maximal mydriasis is reached in 30-40 minutes. Mydriasis may last up to 10 days. Maximal cycloplegia is reached in 60-180 minutes, but 3 days are required to produce complete cycloplegia. Cycloplegia lasts from 7-12 days.[3-6] Ocular side effects are rare and include direct irritation and stinging on instillation most commonly. Systemic effects can occur due to absorption from the conjunctival vessels and the nasal mucosa and are dose dependent. The most common effects are fever, restlessness and hallucinations. Most of these effects generally occur at dosages greater than 20 times the minimum. The susceptibility of each patient does vary. More susceptible groups are infants, elderly, lightly pigmented individuals, individual with spastic paralysis, Down syndrome or brain damage.[4] Atropine is administered as a single drop twice a day for 1-3 days.[1,5]

Cyclopentolate is a water-soluble ester. It has both mydriatic and cycloplegic properties. Maximal mydriasis is reached at 20-45 minutes using a 1% solution. Mydriasis usually lasts 24 hours. Maximal cylopegia is also reached at 20-45 minutes and usually lasts 6-24 hours.[3-5] It is the cycloplegic with the fastest onset and shortest recovery time. It is also the only cycloplegic where maximum onset of cycloplegia approximates maximum onset of mydriasis. This allows the use of the fully dilated pupil to indicate full cycloplegia. The most common ocular side effect is stinging on instillation. Systemic effects are dose dependent. The central nervous system is the most affected and visual and tactile hallucinations can occur. The effects usually subside within 2 hours in adults and 4-6 hours in children without permanent sequelae. Effects are more likely to occur when using higher concentrations in infants, elderly, individuals who have neurological impairment, spastic paralysis or brain damage. Cyclopentolate is administered 30-45 minutes before the examination as 2-3 drops given 5-10 minutes apart.[4,5,6]

An effective cycloplegic agent is essential to cycloplegic refraction. The ideal cycloplegic agent should have a rapid onset with adequate duration of maximum cycloplegia, complete paralysis of accommodation, rapid recovery of accommodation and an absence of side effects.[3] No cycloplegic agent possesses all of these properties and there is no agreement as to which agent is ideal. Atropine is however the gold standard for complete cycloplegia, but it has a difficult administration regimen. It requires a second consultation with instillation 3 days prior to the examination and the effects last from 7-10 days. It requires administration at the patient's residence. This makes compliance an additional factor to consider. It also has more side effects and longer impairment of near vision than cyclopentolate, which has been advocated as an alternative. The shorter acting cyclopentolate has the advantage that the cycloplegic refraction can be performed during the first consultation and the effects usually only last 24 hours.[3,6-8]

Literature Review:

Several studies have compared the effect of cyclopentolate with atropine with regard to refraction to determine if it could be a suitable alternative. However, the literature on this topic is limited. One of the first studies was conducted by Ingram and Barr in 1979 which compared the results of cycloplegic refraction with 1% cyclopentolate to the results of cycloplegic refraction with 1% atropine in 1 year old children. However, the atropine study was conducted by one of the authors in a previous year. Whilst this was not an ideal method to compare the two drugs, the atropine study revealed more hyperopia than the cyclopentolate study indicating that atropine is superior.[9] A crossover study by the author Farhood in 2012 found no overall difference in cycloplegic refraction when comparing the two drugs. It was noted that children younger than 5 years had more hyperopia uncovered by atropine. This result was compared to the findings of Robb and Peterson which also noted more hyperopia being uncovered with atropine in children younger than 6 years, but was in contrast to the findings of Rosenbaum who showed that atropine was probably unnecessary when studying Caucasian esotropic children younger than 5 years. In the study by Farhood the participants were not young enough and were limited to the age group 3-8 years. There was also no detail provided on who performed the retinoscopy and who administered the regimens.[8] Two studies were conducted in Africa. A randomized controlled trial by Ebri et al was conducted in Nigeria on 234 children and published in 2007. Nigerian children between the age 4-15 years were randomized to either 1% cyclopentolate, 1% cyclopentolate and 0,5% tropicamide, or 1% atropine. The study was specific for children with dark irides and was to ascertain if cyclopentolate and tropicamide were as effective as atropine in this population. Mean residual accommodation was measured and was shown to be significantly lower in the atropine group. This study was however too small to find statistically significant differences. The selected participants were also not young enough.[10] The other African study was also conducted in Nigeria and is the most recent study. Sani et al conducted a crossover interventional study and published in 2016. Atropine was compared to a cyclopentolate-tropicamide combination in hyperopic children. It was found that there was a similarity between the cycloplegic refractions of both regimens, although there was no statistically significant difference. The participants were limited to the age of 5-12 years and it was recommended that future studies should include younger children to make findings more reliable as they have a higher amplitude of accommodation and are therefore more in need of cycloplegia.[7]

Cycloplegic refraction in children is routinely conducted at our institution. Atropine is the cycloplegic agent that is prescribed for most children above the age of one as it is the gold standard, although it has the least desirable properties of an ideal cycloplegic agent. Cyclopentolate is the theoretically preferred agent and has been advocated as an alternative. There is evidence that cyclopentolate compares to atropine in efficacy in cycloplegic refraction. However, there is insufficient information

available in the African population and especially so in younger children. It is on this background that a prospective study comparing the two agents in cycloplegic refraction in children is proposed.

2. Hypothesis

Cyclopentolate is not inferior to atropine and should routinely be used for cycloplegic refraction in children

3. Study Aim & Objective

Aim

To investigate the outcome of cycloplegic refraction in children when using atropine as a cycloplegic agent compared with cyclopentolate

Objectives

- To determine if cyclopentolate is as effective as atropine for cycloplegic refraction in dark irides
- To determine if cyclopentolate could be used as an alternative to atropine for cycloplegic refraction

4. Methods

Study Design

This is a prospective, sequential, paired design. Each eye will act as its own control.

Sample Population

40 patients (80 eyes) between the ages of 1-6 years who present to the paediatric ophthalmology clinic at St John Eye Hospital that require cycloplegic refraction will be enrolled into the study. Informed consent will be sought from one of the parents or guardian.

Inclusion Criteria

- Children aged between 1-6 years
- Dark irides

Exclusion Criteria

- Ophthalmic disease that would prevent performing refraction
- Failure to follow up with study visits

Sampling & Sample Size

Patients will be selected at random to ensure that an objective data analysis is obtained in a controlled environment. Patients will be numbered according to presentation. All patients will have cyclopentolate administered initially and then have atropine administered.

Sample size estimation is based on the comparison of the refraction measured with the use of atropine with that obtained with the use of cyclopentolate. This requires the use of a paired t-test. For the detection of small, medium and large effect sizes (dz=0.2, 0.5 and 0.8, respectively) with 80% power at the 5% significance level, sample sizes of 199, 34 and 15, respectively, are required. We typically aim for the detection of at least a medium effect size, should it exist; thus the proposed sample size of 80 eyes for this study is adequate.

Sample size calculations were carried out in G*Power.[11]

Preinstillation Assessment

All patients will be assessed prior to the instillation of cycloplegic agents. A detailed history will be obtained and an ophthalmological examination will be performed. Informed consent will be obtained from the patients' parent or guardian who is willing to participate in this study. A standardized information sheet (Appendix A) and consent form (Appendix B) will be provided.

Study Procedure

On the first visit, patients will have 3 drops of 1% cyclopentolate instilled five minutes apart with refraction after 45 minute. Two weeks later, the same patients will have 1% atropine instilled twice daily for three days before and on the day of refraction.

Only one drop will be administered into the lower fornix of the eye and digital pressure will be applied for a few minutes to the lacrimal puncti. Parents or guardians of patients who will be administering atropine will be explained how to administer the drops in their language of choice by nursing staff.

Refractions will be carried out in a dark room using a retinoscope. Results will be converted into the spherical equivalent of the obtained values.

Data Collection

Results of the cycloplegic refractions will be entered onto a standardised data capture sheet (Appendix C)

5. Data Analysis

Information from the data capture sheets will be entered onto an Excel spreadsheet. Data will be analysed in conjunction with a statistician. Descriptive analysis of the data will be carried out as follows: Categorical variables will be summarised by frequency and percentage tabulation, and illustrated by means of bar charts. Continuous variables will be summarised by the mean, standard deviation, median and interquartile range, and their distribution illustrated by means of histograms.

The comparison of the refraction measured with the use of atropine with that obtained with the use of cyclopentolate will be done using the paired t-test.

Data analysis will be carried out using SAS. The 5% significance level will be used.

6. Ethics

Application for ethics approval from the WITS HREC will be submitted in October 2016. Confidentiality will be maintained by allocating a study number instead of the patient's name. The study number will be used on the data capture form and this number will be utilized for the remainder of the study analysis.

7. Timing

TIMELINE	
October 2016	Protocol Submission
November 2016	Assessment Committee Meeting Ethics Submission
December 2016	Data Collection
January 2017	Data Collection Data Analysis and write-up
February 2017	Write-up
March 2017	Submit for marking
*timeline pending approval of proposal and ethics committee permission	

8. Reporting Plans

The results of this study will be presented to the Ophthalmic Society of Southern Africa and published in an ophthalmology journal.

9. Funding

Cycloplegic refraction is performed routinely at our institution therefore this study would be utilizing already existing drugs and equipment. Any additional costs will be covered by the researcher.

10. Limitations

Atropine will be administered at home by patients' parents or guardians and compliance may be an issue.

11. Authorship

Author: Dr Divashini Kisten

Supervisor: Prof I Mayet

12. References

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10. Ebri A, Kuper H, Wedner S. Cost-Effectiveness of Cycloplegic Agents: Results of a Randomized Controlled Trial in Nigerian Children. Invest Ophthalmol Vis Sci. 2007 Mar; 48(3): 1025-1031.
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APPENDIX A

INFORMATION SHEET

Translation of information to your language of preference may be carried out by nursing staff at St John Eye Hospital

A Comparison Between Atropine and Cyclopentolate in Cycloplegic Refraction in Children

Good day, my name is Dr Divashini Kisten and I am training to be an eye doctor in the Department of Ophthalmology at the University of Witwatersrand. My training requires me to do research in this field. Research is a process that allows us to learn more about a question that we don't have the answer to.

In this study I would like to determine which medication allows a better assessment of your child's vision in our routine vision test for glasses. The medication is necessary to allow a proper evaluation of your child's eye sight. We usually use eye drops called atropine. These drops can last up to 2 weeks in the eye. There is another eye drop called cyclopentolate which only lasts up to 1 day in the eye. I would like to see if this eye drop works as well as atropine.

I would like your permission to include your child in this study which will be conducted at St John Eye Hospital.

This study will involve your child having 2 vision tests for glasses. They will be 2 weeks apart. At the first visit, the vision test will be done using the eye drop cyclopentolate. I will put the drops in your child's eye at the hospital. It takes 45 minutes for the drops to work. I will then do the vision test for your child.
The next vision test will be done 2 weeks later using our usual eye drop which you will use at home according to its usual procedure. You will put 1 drop into each eye twice a day. This will be done for three days before and on the day of the vision test. You will then come to the hospital where I will do the vision test for your child. The eye drop will be placed under the lower eyelid and then you will place your finger at the corner of the child's eye close to the nose for a few minutes.

Both of these eye drops are used routinely around the world for the vision test. They are both safe to use in children. Rarely, some children do experience side effects from the medication. If you are using our usual eye drops at home and notice that your child has a fever or is behaving differently to normal or if you have any concerns then you should bring the child back to the hospital immediately for us to assist you. The other drops that will be put in the hospital will be done in a controlled environment and if any problems do occur we will be able to assist you.

A benefit to being in this study is that your child receives two vision tests on two separate occasions allowing a more accurate assessment of your child's eye sight.

Your child's identity will remain confidential during and after the study. A study number will be assigned to your child in place of the name. Your child's details and examination findings will be recorded using the study number. This information will be seen by me, the statistician and the medical fraternity. If at any point you choose to withdraw from this study, you may do so immediately and without reason or consequence and your withdrawal will not impact on your future health care at our facility.

Contact Details of researcher:
Dr Divashini Kisten
(011) 933 8783

REC Administrator and Chair
The study has been approved by the Wits HREC (Medical). Any queries or questions regarding your right as a research participant please contact:
Prof Peter Cleaton-Jones
(011) 717 2301
Ms Z Ndlovu
011 717 2700/1234/1252

Thank you for taking the time to read this information sheet.

APPENDIX B



CONSENT FORM

I, _____ (parent/guardian), hereby consent to

_____ (child) voluntarily participating in this study. Dr Divashini Kisten has clearly informed me and pointed out the purposes of the research she will be conducting. I have read and understand the information sheet provided to me, which clearly explains the procedure and its risks.

- I am aware that I do have the right not to participate or to discontinue participation at any time without prejudicing any treatment that is required for existing or future medical conditions.
- Patient confidentiality will be maintained at all times meaning that information may be used from my file as long as my name is not mentioned.
- The documents completed by Dr Kisten are the only records that will be used for data collection.
- If I have any queries, they will be directed accordingly.

GUARDIAN OF ENROLLED PATIENT

_____	_____	_____
Full name and Surname	Date	Signature

_____

STUDY DOCTOR:

I, Dr Divashini Kisten hereby confirm that I have fully informed the participating patient of the nature and purposes of my study.

_____	_____	_____
Full name and Surname	Date	Signature

_____

WITNESS

_____	_____	_____
Full name and Surname	Date	Signature

APPENDIX C

DATA COLLECTION SHEET

Study Number	**Age**	**Gender**	**Race**

Other medical conditions

☐ No

☐ Yes, specify: _____

Medication Usage

☐ Topical: _____

☐ Oral: _____

Allergies

☐ No

☐ Yes, specify: _____

Cycloplegic Refraction	RE	LE
Cyclopentolate 1% Date:		
Atropine 1% Date:		

	Cyclopentolate 1%	Atropine 1%
Reported Adverse Effects	☐ Local: _____	☐ Local: _____
	☐ Systemic: _____	☐ Systemic: _____

Appendix B: Ethics clearance certificate

R14/49 Dr Divashini Kisten

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M161162

NAME: (Principal Investigator)	Dr Divashini Kisten
DEPARTMENT:	Neurosciences, Ophthalmology Chris Hani Baragwanath Academic Hospital St John Eye Hospital
PROJECT TITLE:	A Comparison between Atropine and Cyclopentolate in Cycloplegic Refraction in Children
DATE CONSIDERED:	25/11/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof I Mayet
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/01/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Permission letters

Consent to Allow for Collection of Data for the Purposes of Research

To whom it may concern,

This document hereby serves as permission for Dr Divashini Kisten, student number 0501023M, to collect the relevant data needed to complete the research intended under the title:

A Comparison Between Atropine and Cyclopentolate in Cycloplegic Refraction in Children

Data will be collected prospectively in the Ophthalmology department at St John Eye Hospital. Collection methods will be as per the submitted protocol and information will remain strictly confidential to the author. All data collection will be performed after approval by the Human Research Ethics Committee of the University of the Witwatersrand.

The intended research will not interfere with the daily running of the hospital.

Head of Department Ophthalmology CHBAH

Name G. D. McHaven Date 11/10/2016

Signature

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 27 Oct 2016

TITLE OF PROJECT: A comparison between atropine and cyclopentolate in cycloplegic refraction in children

UNIVERSITY: Witwatersrand

Principal Investigator: D Kisten

Department: Ophthalmology

Supervisor (If relevant): I Mayet

Permission Head Department (where research conducted): Yes

Date of start of proposed study: Oct 2016
Date of completion of data collection: Dec 2017

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 27 October 2016

.....
Approved/Not Approved
Hospital Management
Date: 31/10/16

Appendix D: Turnitin Report

0501023m:MMED(Final)-
_A_Comparison_Between_Atropine_and_Cyclopentolate_in_..

ORIGINALITY REPORT

32%	6%	5%	30%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	26%
2	Farhana Kalam, Mohammad Omar Faruq, Saleha Begum Chowdhury. "Maternal and perinatal mortality, morbidity and risk factor evaluation in ante partum hemorrhage associated with Placenta Praevia", Bangladesh Critical Care Journal, 2013 Publication	1%
3	spangsdorf-staal.dk Internet Source	1%
4	www.iovs.org Internet Source	1%
5	Submitted to University of Sheffield Student Paper	1%
6	E.L. Miller. "Disk Infant Mortality in Large Storage Systems", 13th IEEE International Symposium on Modeling Analysis and	1%

*Student Paper submitted refers to the protocol submitted in preparation for research report.

Acknowledged by Prof I Mayet (Supervisor): _____