Study Protocol

Assessing the Efficacy of Low-Dose Topical Atropine (0.01%) for Controlling the Progress of Myopia Among School Children

Abstract:

Background: It is one of the most common abnormalities of human eyes and its incidence has dramatically risen in incidence in the last few decades. Myopia may lead to irreversible vision loss. A number of studies reflect on the effectiveness of low concentration atropine in controlling myopia. Atropine is used topically as a cycloplegic for the accommodation reflex and as a mydriatic for pupillary dilatation. Since myopia is leading cause of diminution of vision in early childhood, use of atropine (0.01%) in early stages can provide regression in myopic changes in eye. This study aimed to assess the change in spherical equivalent, changes in axial and keratometry values and retinal degenerative changes in cases of myopia treated with low dose atropine.

Methodology: The enrolled cases of myopia will undergo thorough ophthalmological examination and will be randomized into intervention and control groups. All cases in intervention group will be treated with low dose atropine (0.01%) eye drops at night and will be followed up every 6 months for examination. The control group will be provided refractive spectacles and also followed up every 6 months. The data from both groups will be compared and analysed.

Expected Results- Significant reduction in the progression of Myopia among school going children is expected with administration of 0.01% atropine eye drops.

Conclusion: Use of atropine (0.01%) in early stages can provide regression in myopic changes in eye.

Keywords- Children, Vision, Myopia control, low dose atropine (0.01%),

Introduction:

Myopia or nearsightedness, is a type of refractive error characterized by discrepancy between optical power and axial length of the eyeball leading to focusing of light just before the retina. Myopia is the condition in which parallel light rays from infinity, as they refract on cornea and lens, intersect at a focal point just before the retina when the accommodation is at rest. [(1)]

It is one of the most common abnormalities of human eyes and its incidence has dramatically risen in incidence in the last few decades. It was included as a priority in the 'Vision 2020' initiative by the World Health Organization's Global Initiative for the

Elimination of Avoidable Blindness because it has become a public health problem. According to recent reviews, it has been projected that approximately 2.5 billion people are likely to develop Myopia by the year 2020. [2]

Recent evidence indicates an increasing prevalence of myopia. There is also a tendency to be seen in the younger population over the last 20 to 30 years. [3-5]

The most prevalent form of myopia worldwide is axial myopia which is caused because of the lengthening of the axial length of the eyeball.

Increase in the axial length starts during childhood, especially during adolescent growth period and an increase in axial length proportionally increases the risks of myopia related complications.

The increased axial length considerably enhances the risk of degenerative changes in retina including chorioretinal atrophic patches at the macula, Foster-Fuchs' spot, cystoid degeneration, lattice degeneration, total retinal atrophy, posterior staphyloma.

Preventing myopia progression during childhood is the most effective way to decrease myopia related complications in children. One of the principal causes of vision loss is the lack of correction of myopia.

Presently, the fundamental mechanism for the progression and development of myopia remains ambiguous; nonetheless, it has been discerned that the environment and individual genetics play a major role in determining the axial length. [6]

There is strong evidence to point that the optical environment plays a major role in determining the axial length. Gene therapy might be used in the future to determine the increase in axial length. [3, 7, 8]

As determined by the Sydney Myopia Study outdoor activity is a protective factor against myopia progression, activities involving near distance work have a poor effect, even when parental myopia and ethnicity have been accounted for. [9, 10]

Myopia is said to be the sixth most important causation of vision loss and it has been observed among young adults that most of the myopia related complications have started manifesting among them. [3, 11]

In a population-based cross-sectional study, The Central India Eye and Medical Study which was conducted in a rural area located approximately 40 km from Nagpur and it learnt that the prevalence of myopia(>0.5D) was 17.0+0.6%.

Prevalence of myopia of more than -1.0 D was 13.0+0.5% and more than -6.0 D, was 0.9-1.4% High myopia, greater than 8 D, was found in 0.4-0.1% of the subjects. [12]

Another study dictated that amongst children in schools aged 5 to 15 years old, the prevalence of myopia was 3.4 %. [13]

This drug is a competitive and non-selective antagonist of the muscarinic acetylcholine receptors.

Atropine is used topically as a cycloplegic for the accommodation reflex and as a mydriatic for pupillary dilatation.

Background and rationale:

Myopia is the most widespread refractive error present. Distant objects remain blurred in the uncorrected state because of anterior focusing of these rays in front of the retina. The distant point of the eye recedes to a finite point. Because of myopia, objects appear to be out of focus and may lead to headaches and eyestrain. [15-17]

Myopia is classified as Simple and Pathological

Based on the diopteric power of the corrective lens used, myopia is classified as low, moderate and high. Myopia is treated by optical correction. Concave lenses with the required minus power is the treatment of choice

Atropine sulphate is the sulphate salt of atropine(Alkaloid) a derivative of Atropa belladonna. It can be derived from other plants of the Solanaceae family as well namely Datura stramonium, Mandragora officinarum, and Hyoscyamus niger. (18)

Structure- It is composed of tropine (organic base) and tropic (an aromatic) which join together to form an organic ester.

Mechanism of Action- atropine is a nonselective and an anti-muscarinic receptor agonist. It has an affinity for the 5 subtypes of muscarinic acetylcholine receptors which are M1 to M5 receptors.

EFFECTS AND DURATION OF ACTION OF TOPICAL APPLICATION (1%)-

1. Mydriasis- It is the dilation of pupils and it starts in 30 min and completely terminates in 7 to 10 days

2. Cycloplegia- It is the paralysis of ciliary muscles leading to loss of accommodation. Starts in 40min and completely terminates in 10 days to 2 weeks.

Side Effects – they include sensitivity to light (temporary) and blurring of near vision. Exposure to increased levels of ultraviolet light for a long term may be harmful to the retina and the lens which is yet to be seen in any literature.

ROLE IN REDUCING MYOPIA PROGRESSION

A variety of mechanisms have been hypothesised regarding but none of them have been able to completely explain the exact mechanism by which atropine reduces eyeball growth.

It was postulated that the mechanism by which atropine exerts its action on smooth ciliary muscles by cycloplegia and blocks the accommodative function of the eye but this was refuted in animal studies where even after the optic nerve was sectioned or Edinger–Westphal nucleus was destroyed development or recovery of experimental myopia was not inhibited.[19]

It was suggested in a study that atropine might be effective by alteration of the process of retinal neurotransmission due to presence of muscarinic receptors in amacrine cells of the retina but even when cholinergic amacrine cells were destroyed, axial elongation took place and was not inhibited by atropine. [20]

It was suggested that ocular growth inhibition might be mechanistically linked to choroidal thickening due to the fact that atropine leads to cause rapid and transient thickening of choroid and the choroid has a vital role in emmetropization by the process of modifying the thickness as well as changing the retinal image plane when the image defocused. [21]

RATIONALE

Since myopia is leading cause of diminution of vision in early childhood, use of atropine (0.01%) in early stages can provide regression in myopic changes in eye. This kind of study has not been done yet in this region, therefore, we want to conduct this study.

Similar studies that have conducted elsewhere have proven the effectiveness and advantages of using variety of low concentrations of atropine for controlling myopia progression.

Hence we will be undertaking this study to prove the clinical effectiveness and efficacy of using low dose atropine (0.01%) to reduce the progression of myopia in Indian youth.

Objectives:

1. To study the change in spherical equivalent in cases of Myopia control and treated with low dose atropine

2. To study the changes in axial length in cases of Myopia control and treated with low dose atropine

3. To study the changes in keratometric values in cases of Myopia control and treated with low dose atropine

4. To study the retinal degenerative changes in cases of Myopia control and treated with low dose atropine

Trial design: Case-Control Comparative Study.

Methodology:

- The study will follow the principles of the Helsinki Declaration, and approval from the institutional ethics committee of DMIMSU will be taken.
- All subjects will be explained the purpose and potential implications of the study and informed consent will be taken from them.
- SETTINGS: All the procedures will be conducted at the Department of Ophthalmology in Acharya Vinoba Bhave Rural Hospital (AVBRH), Sawangi.
- RESEARCH DESIGN: Prospective, Randomized comparative study
- PARTICIPANTS: All patients with myopia coming to Ophthalmology department of AVBRH will be selected for the study after taking inclusion and exclusion criteria into consideration.
- INCLUSION CRITERIA:
    1. Age: 6 years -15 years
    2. Myopia ≥ 2.00 D (cycloplegic refraction; spherical equivalent)

3. No prior or current treatment for preventing myopia progression (bifocals / progressive addition lenses / orthokeratology)
4. Patients willing to participate in the study will be eligible for inclusion.

- EXCLUSION CRITERIA:
  1. Refractive Myopia
  2. Best corrected visual acuity < 6/12
  3. Astigmatism ≥ 1.5 D
  4. Ocular hypertension / Glaucoma
  5. Amblyopia
  6. Topical atropine eye drops allergy
  7. History of previous intraocular surgery
  8. Systemic diseases associated with myopia including Stickler syndrome, Marfan syndrome,etc
  9. Patients with cardiac or severe respiratory disorders
  10. Lack of consent for participating in the study

Sample size:

Sample Size formula with desired error of margin

$$n = \frac{(Z_{\alpha/2})^2 . P. (1-P)}{d^2}$$

Where;

Z_α is the level of Significance at 5% i.e. 95%.

Confidence interval =1.96

P= Prevalence of Myopia in school going children [13] = 3.4% = 0.034

d= Desired error of margin = 4% = 0.04

$$n = \frac{1.96^2 \text{ X } 0.034 \text{ X } (1-0.034)}{0.04\%}$$

= 78.85

= 80 patients needed in each group

Methods:

Data collection methods:

The study will follow the principles of the Helsinki Declaration, and approval from the institutional ethics committee of DMIMSU will be taken. Patients with myopia presenting to the Ophthalmology OPD will be selected based on the inclusion and exclusion criteria. All patients will be explained the nature of the study and an informed consent will be taken from them. Consent will be in local language to ensure validity. Patients will undergo a comprehensive ophthalmological test, including best-corrected visual acuity, slit-lamp examination and IOP calculation will be performed on all patients. Autorefractometry, streak retinoscopy and keratometry will be will be done. Subjective Refraction will be done for every patient and spectacles will be given to the patient for constant use. Fundus examination post pupillary dilatation with Tropicamide will be done**.** Axial length measurement will be taken using A-Scan**.** Case group patients will be prescribed Atropine (0.01%) eye drops to be administered one drop in both eyes at night. Control group patients will be prescribed only refractive spectacles. Patients will be advised to come to OPD for follow up after 6 months, 1 year, 1.5 years and finally at 2 years. Refraction and axial length will be done for both cases and control group patients at every follow up visit. Correlation of all data will be done.

Statistical methods: Statistical analysis will be done by using statistics in terms of differential and inferential method using chi square test, students square T test and unpaired T test analysis will be done, $p<0.05$ will be considered as level of significance.

Expected Outcomes/Results:

This is a prospective randomized case control study of 200 patients assigned to treatment with low dose atropine (0.01%).All patients in both the case and control groups will have a 6 monthly follow up for a period of 2 years. Study parameters will be compiled and cases and controls will be compared.

The study will be done for a period of two years (January 2020 to January 2022) at AVBRH hospital. Institutional Ethical Committee permission will be taken. Informed consent will be obtained from each patient.

Discussion:

There are several clinical trials to support the impact of atropine in slowing eye development, however there is a lack of understanding of the mechanism leading to reduced elongation along the axial axis of the eye and the site of action.

The Atropine for the Treatment of Myopia 1 (ATOM 1), a randomized controlled trial involving 400 children in the age group 6 to 12 years over a period of 2 years , established that 1% atropine eye drops reduced myopia progression to -0.28+0.92 diopters (D), compared with -1.20+0.69 D in the placebo group, with a 77% decrease in myopia progression with no axial elongation. [(22)]

It is possible to effectively monitor the development of myopia in children by administering low-dose atropine eye drops. Atropine's success in regulating the development of myopia is

dose-dependent. Higher doses have been found to be more effective, but higher doses appear to be associated with increased side effects such as photophobia, poor near vision, and rebound effects after atropine cessation, which are seen at higher doses. Low dose of atropine does not lead to these side effects. [23, 24]

Moderate and low dosage concentrations of atropine (0.01%, 0.025%, 0.05%, and 0.1%) have shown positive results in controlling myopia progression in children with least number of side effects, convenience in use and rare rebound effects post discontinuation. In a study conducted by Yam et al and Moon and Shin, it was reported that different atropine doses had varying progression effects on myopia with 0.01 percent, 0.025 percent and 0.05 percent atropine administration, but the dose-dependent side effects were only in the study of Yam et al, contrary to Moon and Shin study where these effects were not seen. [23-28]

According to the ATOM2 study that was conducted over a 5-year follow-up period, the high effectiveness of low-dose atropine was exhibited at a concentration of 0.01 percent in delaying advancement of myopia with less visual side effects in comparison with higher doses of atropine. As a way of successful management of myopia, 0.01 percent atropine is much more tolerable and suitable for patients. [25, 30]

Since myopia is leading cause of diminution of vision in early childhood, use of atropine (0.01%) in early stages can provide regression in myopic changes in eye. This kind of study has not been done yet in this region, therefore, we want to conduct this study.

Similar studies that have performed elsewhere have shown the effectiveness and benefits of using various low doses of atropine for myopia. Few of the related studies were reviewed [31-36]. Related cases were also reported by Mulet et. al. [37] and Shaikh et. al. [38-41].

We will therefore conduct this research to demonstrate the clinical effectiveness and efficacy of low-dose atropine (0.01 percent) in reducing myopia advancement in Indian adolescents.

Limitations

- This research has a limited sample size and needs a larger sample size to validate these outcomes
- Short follow up period for each subject.

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