

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 Myopia 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

Comment [M1]: General comments
1. Provide continuous line numbers
2. Add some more literatures in the introduction
3. Merge background and rationale in to introduction. Conclude the introduction session by putting objectives
4. Follow the manuscript write-up protocol such as Abstract, introduction, methodology, result, discussion and references
5. Was the study completed or not yet? The whole manuscript seems proposal please rewrite it. If it is manuscript, use past tense, not future tense during narration

Comment [M2]: Replace it with "Myopia"

Comment [M3]: Remove it

Comment [M4]: It should be "was"

Comment [M5]: Replace it by "was found"

Comment [M6]: Add it

Comment [M7]: Remove it

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

Comment [M8]: But I don't know when this study has conducted. So you should set your study period.

42 Recent evidence indicates an increasing prevalence of myopia. There is also a tendency to
43 be seen in the younger population over the last 20 to 30 years. ⁽³⁻⁵⁾

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

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

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

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

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

58 There is strong evidence to point that the optical environment plays a major role in
59 determining the axial length. Gene therapy might be used in the future to determine the
60 increase in axial length. ^(3, 7, 8)

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

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

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

Comment [M9]: Make it short by removing unnecessary narrations i.e. a study from India revealed that the prevalence of myopia was...

70 Prevalence of myopia of more than -1.0 D was 13.0+0.5% and more than -6.0 D, was 0.9-
71 1.4% High myopia, greater than 8 D, was found in 0.4-0.1% of the subjects. ⁽¹²⁾

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

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

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

Comment [M10]: Relocate this statement before line 74

78

79 **Background and rationale:**

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

84 Myopia ~~is classified~~ can be Simple or Pathological. Furthermore, based on the dioptric
85 power of the corrective lens used, myopia is classified as low, moderate and high. Myopia is
86 treated by optical correction. Concave lenses with the required minus power is the
87 treatment of choice

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

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

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

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

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

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

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

104 ROLE IN REDUCING MYOPIA PROGRESSION

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

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

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

Comment [M11]: Merge this into introduction and remove redundant statements

Comment [M12]: Link these statement with the coming one

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

120 **RATIONALE**

121 Since myopia is leading cause of diminution of vision in early childhood, use of atropine
122 (0.01%) in early stages can provide regression in myopic changes in eye. This kind of study
123 has not been done yet in this region, therefore, we want to conduct this study.

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

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

129

130 **Objectives:**

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

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

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

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

139 **Trial design:** Case-Control Comparative Study.

140

141 **Methodology:**

142 • The study will follow the principles of the Helsinki Declaration, and approval from the
143 institutional ethics committee of DMIMSU will be taken.

144 • All subjects will be explained the purpose and potential implications of the study and
145 informed consent will be taken from them.

146 • **SETTINGS:** All the procedures will be conducted at the Department of Ophthalmology in
147 Acharya Vinoba Bhave Rural Hospital (AVBRH), Sawangi.

148 • **RESEARCH DESIGN:** Prospective, Randomized comparative study

149 • **PARTICIPANTS:** All patients with myopia coming to Ophthalmology department of
150 AVBRH will be selected for the study after taking inclusion and exclusion criteria into
151 consideration.

152 • **INCLUSION CRITERIA:**

153 1. Age: 6 years -15 years

154 2. Myopia \geq 2.00 D (cycloplegic refraction; spherical equivalent)

Comment [M13]: This is part of Ethics and consent to participate which is better to write at the end of the manuscript.

Comment [M14]: It lacks time specification so you may say all patients with myopia coming to AVBRH during data collection period were study participants.

Comment [M15]: Already done, say were

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

158
159 • **EXCLUSION CRITERIA:**

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

171 **Sample size:**

172 Sample Size formula with desired error of margin

173
$$n = \frac{(Z_{\alpha/2})^2 \cdot P \cdot (1-P)}{d^2}$$

174
175 Where;

176 Z_{α} is the level of Significance at 5% i.e. 95%.

177 Confidence interval = 1.96

178 P= Prevalence of Myopia in school going children ⁽¹³⁾ = 3.4% = 0.034

179 d= Desired error of margin = 4% = 0.04

180
181
$$n = \frac{1.96^2 \times 0.034 \times (1-0.034)}{0.04^2}$$

182
183 = 78.85

184
185 = 80 patients needed in each group

186
187
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189
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193 **Methods:**

194 Data collection ~~methods:~~ procedures

195 The study will follow the principles of the Helsinki Declaration, and approval from the
196 institutional ethics committee of DMIMSU will be taken. Patients with myopia presenting to

Comment [M16]: Avoid it. Note that under methodology session, there are study area & setting, selection criteria, sample size determination, sampling technique, data collection tools and criteria, operational definition and statistical analysis

Comment [M17]: Add it

Comment [M18]: This is Part of ethics, not part of it

197 the Ophthalmology OPD will be selected based on the inclusion and exclusion criteria. All
198 patients will be explained the nature of the study and an informed consent will be taken
199 from them. Consent will be in local language to ensure validity. Patients will undergo a
200 comprehensive ophthalmological test, including best-corrected visual acuity, slit-lamp
201 examination and IOP calculation will be performed on all patients. Autorefractometry,
202 streak retinoscopy and keratometry will be will be done. Subjective Refraction will be done
203 for every patient and spectacles will be given to the patient for constant use. Fundus
204 examination post pupillary dilatation with Tropicamide will be done. Axial length
205 measurement will be taken using A-Scan. Case group patients will be prescribed Atropine
206 (0.01%) eye drops to be administered one drop in both eyes at night. Control group patients
207 will be prescribed only refractive spectacles. Patients will be advised to come to OPD for
208 follow up after 6 months, 1 year, 1.5 years and finally at 2 years. Refraction and axial length
209 will be done for both cases and control group patients at every follow up visit. Correlation of
210 all data will be done.

Comment [M19]: This is Part of ethics and consent, not part of it

211

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

215

216 **Expected Outcomes/Results:**

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

Comment [M20]: Better to say results. Your findings are narrowly explained I suggest you to expand the result session and discussion without a sound result is nothing.

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

Comment [M21]: It is part of ethics and consent

224

225 **Discussion:**

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

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

Comment [M22]: Are they your sample size?

234 It is possible to effectively monitor the development of myopia in children by administering
235 low-dose atropine eye drops. Atropine's success in regulating the development of myopia is
236 dose-dependent. Higher doses have been found to be more effective, but higher doses
237 appear to be associated with increased side effects such as photophobia, poor near vision,

238 and rebound effects after atropine cessation, which are seen at higher doses. Low dose of
239 atropine does not lead to these side effects. ^(23, 24)

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

Comment [M23]: Replace the word percent by % in the whole document

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

252 Since myopia is leading cause of diminution of vision in early childhood, use of atropine
253 (0.01%) in early stages can provide regression in myopic changes in eye. This kind of study
254 has not been done yet in this region, therefore, we want to conduct this study.

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

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

261 **Conclusion**

Comment [M24]: Conclusion????

262 **Limitations**

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

266

267 **REFERENCES**

Comment [M25]: Reduce using old references

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