10.5935/0034-7280.20180015

Decrease of myopia progression with 0.025% atropine

Diminuição da progressão da miopia com atropina 0,025%

Celso Marcelo da Cunha[1], Renato José Bett Correia[2], Jéssica Teixeira Cunha[3]

ABSTRACT

Purpose: *To demonstrate the efficacy of 0.025% atropine eyedrops in myopic children in Brazil for decreasing myopia progression* ***Methods:*** *This was a prospective study with 60 children from Hospital Geral Universitário and Oftalmocenter Santa Rosa in Cuiabá, MT, Brazil, aged between 6 to 12 years, with spherical equivalent refractive error of -1.00 to -6.00 diopters (D) and astigmatism of -1.00 D or smaller. They underwent a complete ophthalmological examination, corneal topography and optical biometry. Children were assigned into two groups: group 1 used 0.025% atropine drop, once-nightly dosing, and it was prescribed total refraction in anti-reflective coating lens; and group 2 was prescribed just total refraction. A new evaluation was conducted 2 years after that. Paired student's t-test was used to compare refractions, axial length and keratometry which were measured in an initial exam and after a two-year follow-up.* ***Results:*** *Of the 60 children, the 30 in group 1 had an age mean and SD 8.21 +/- 1.72, and of the control group were 8.17 +/- 1.73 years. Fourteen (46,66%) and 16 (53,33%) were male, respectively. Myopic progression was significantly lower in group 1 (-0.43 +/- 0.19 D) than in group 2 (-1.24 +/- 0.37 D) and axial length increase was also significantly smaller in group 1(0.19 +/- 0.09 mm) than in group 2 (0.48 +/- 0.12 mm). There were no significant statistical differences regarding keratometry between groups.* ***Conclusions:*** *Low dose atropine eyedrops were effective in decreasing myopia progression in 65% of this population studied for 2 years. Furthermore, a larger scale randomized controlled study with longer follow-up seems warranted.*

Keywords: *Refraction errors; Myopia; Atropine*

RESUMO

Objetivo: Demonstrar a eficácia do uso do colírio de atropina 0,025% em crianças míopes, no Brasil, para a diminuição da progressão da miopia. **Métodos:** Realizou-se estudo prospectivo em 60 pacientes do Hospital Geral Universitário e Oftalmocenter Santa Rosa - Cuiabá - MT, com idades entre 6 e 12 anos, com equivalente esférico da refração entre -1,00 a -6,00 DE, refração cilíndrica < -1,00 DC e taxa de progressão anual de 0,50 DE (ou maior). Efetuou-se exame oftalmológico geral, topografia corneana e a medida do diâmetro anteroposterior do globo ocular (DAP). Os pacientes foram divididos em dois grupos: em que o Grupo 1 recebeu colírio de atropina 0,025%, todas as noites, e prescreveu-se a refração total com lentes com antirreflexo de multicamadas; e, no Grupo 2, somente a refração total. Nova avaliação foi realizada dois anos após. O teste T Student pareado foi utilizado para comparações das refrações, DAP e ceratometrias, medidas no exame inicial e no exame com 2 anos de seguimento. **Resultados:** Das 60 crianças, 30 eram do Grupo 1 com idade média de 8,21 ± 1,72 anos, e as do grupo controle com idade média de 8,17 ± 1,73 anos. Quatorze (46,66%) e 16 (53,33%) eram do sexo masculino nos Grupos 1 e 2, respectivamente. O Grupo 1 revelou menor progressão da miopia (Grupo 1: 0,43 ± 0,19D, Grupo 2: 1,24 ± 0,37D) e menor crescimento do DAP em relação ao grupo controle (Grupo 1: 0,19 ± 0,09mm, Grupo 2: 0,48 ± 0,12mm). Houve diferença estatisticamente significativa (P<0,05) entre o grupo tratado e o controle em relação à refração e ao crescimento DAP. A topografia não teve mudança estatisticamente significativa. **Conclusão:** A atropina em baixas concentrações foi eficaz em diminuir a progressão da miopia em 65% desta população estudada, por 2 anos. No entanto estudos com maior número de participantes e em diversas regiões do Brasil poderiam demonstrar melhor esse fato.

Descritores: Erros de refração; Miopia; Atropina

[1] Oftalmocenter Santa Rosa, Cuiabá, MT, Brasil.
[2] Hospital Geral Universitário, Cuiabá, MT, Brasil.
[3] Academic Course in Medicine, Centro Universitário da UNIVAG, Várzea Grande, MT, Brasil.

The authors declare no conflict of interests.

Received for publication 21/08/2017 - Accepted for publication 07/01/2018.

Introduction

The prevalence of myopia is variable in different regions of the world. In Asian countries such as Singapore, Taiwan and Hong Kong, there are studies showing alarming increases, finding a prevalence of myopia among youngsters close to 80%. [1-3] In turn, studies in the US and European countries have shown smaller increases, however significant in recent decades. [4,5] The rapid growth in the prevalence of myopia has suggested the involvement of environmental factors, such as the extensive use of near sight and low exposure to outdoor environments, and such growth could not be explained by genetic involvement alone.[6-8]

Studies in the world literature have been developed for several decades on ways to control the progression of myopia.[9,10] Of these, the first studies were with atropine eyedrops, a non-selective muscarinic antagonist agent. Almost all the studies demonstrated a decrease in the progression of myopia in relation to the decrease in the anteroposterior growth of the ocular globe.[11] Besides this way of control, there are several ways of controlling the progression of myopia, and they can be didactically organized in optical, pharmacological and environmental controls. The optical ones are represented by the use of glasses with bifocal or progressive lenses, bifocal contact lenses, and orthokeratology (e.g. Ortho-K). Pharmacological controls use an atropine eyedrops, as mentioned, pirenzepine, as well as the oral use of 7-methilxanthine. The environmental forms of control, in turn, are mainly related to greater exposure to sunlight. These forms of control are clinically important when at least 40% of progression is prevented.[12,13] In the present article about these forms of control, more emphasis is given to the use of atropine eyedrops, since it has demonstrated high potential as a first choice treatment.

The control with atropine is dose-dependent. The higher the concentration, the greater the progression control.[14] The use of atropine 1% in daily doses for 2 years showed almost no progression in children.[11] Unfortunately, however, side effects are also dose dependent, and most of the older studies used high concentrations of atropine and thus led to high rates of side effects and significant withdrawal rates. Photophobia, glare and withdrawal of accommodation are the most frequent side effects, which decrease with the use of progressive photosensitive lenses. Other side effects such as headache, febrile state, hallucinations, saliva decrease, follicular conjunctivitis, allergies are less frequent, but these are the ones to increase those withdrawal rates.[11]

To further discourage the use of atropine 1%, intense rebounds following atropine interruption were reported, and it was noted that, in this situation, progression values in one year almost matched the placebo group.[15] These facts corroborated the poor use of this way to control myopia for decades. In recent years, some studies with low concentrations of atropine called the attention of the world ophthalmology, and one of the main ones was ATOM 2, which used atropine in different concentrations and showed that even with 0.01% it was possible to control 50% of the myopia progression and, even better, almost without side effects and with no significant rebound effect.[14,16]

Low atropine concentrations are considered to be doses below 0.02%, because at these doses it would not significantly alter the accommodation to require further correction for near sight nor cause photophobia.[17] Another study was proposed in 2010 with fewer participants and with 0.025%, and low rates of side effects were also found.[18]

In Brazil, recent publications have revealed tolerance to the use of atropine 0.025% without photosensitive lenses, and using only multilayer antireflex lenses (20 in total. The one-year follow-up demonstrated greater control when compared to the group with photosensitive lenses.[19,20]

In the present study, the progression of myopia in children with the use of atropine 0.025% eyedrops without photosensitive lenses was compared to the control group.

Methods

A longitudinal and prospective non-randomized study was carried out at the ophthalmology clinics of Hospital Geral Universitário e Oftalmocenter Santa Rosa - Cuiabá, MT. The study was registered in Brazil platform and approved by the ethics committee. Patients with initial age between 6 and 12 years were included.

Sixty patients were consecutively selected during the period from January to April 2015 in the ambulatories of the first two authors of this article, after the parents or legal representatives were informed about the informed consent term and approved it. Patients with visual acuity ≥0.07, spherical refractive equivalent from -1.00 to -6.00 DE, cylindrical refraction <-1.00 DC, and annual progression rate of ≥ 0.50 DE (determined by the verification of previous glasses and prescriptions) were included. We excluded candidates who did not meet the inclusion criteria, with anisometropia greater than 1.50 DE, altered rest of the general ocular examination, irregular, premature, syndromic astigmatism, neuropsychomotor changes, and those who interrupted eyedrops for more than 10 following days or had incomplete follow-up.

A general ophthalmologic examination was performed with visual acuity measurement with and without optical correction, as well as coverage test, ocular motility assessment, biomicroscopy of the anterior segment, ocular tonometry, indirect binocular funduscopy, and objective refraction with 5 consecutive measurements with a Canon auto-refractor after 40 min of cycloplegia, preceded by anesthetic eyedrops (Proparacaine 0.5%), followed by 2 drops of cyclopentolate 1% with a 5-min interval and 2 drops of tropicamide 1%. We also evaluated computerized keratoscopy and the measurement of the anteroposterior diameter of the ocular globe with optical biometer (DAP). Patients were evaluated for correct medication use, visual acuity, and non-cycloplegia refraction every four months. Further complete exams were performed yearly as the initial exam.

Patients were divided into two groups as follows:

Group 1: received atropine 0.025% eyedrops every night, and total refraction was prescribed with multilayer antireflective lenses.

Group 2: had total refraction with colorless lenses.

The atropine 0.025% eyedrops were prepared at the local manipulation pharmacy.

Statistical analysis was performed using the software SPSS for Windows (Statistical Package for Social Sciences, version 9.0, SPSS Inc., Chicago, USA). The continuous variables were compared using the Student's t-test, and the categorical variables using the chi-square test. The longitudinal changes for each parameter (refraction, keratometry and DAP) were analyzed with the Student's t-test, comparing these initial results to those of two years of follow-up. P <0.05 was considered statistically significant.

Results

Of the 60 patients, 14 (46.66%) and 16 (53.33%) were male in Groups 1 and 2, respectively. The average initial age was 8.21 ± 1.72 and 8.17 ± 1.73 years, and the average initial myopia was -3.63 ± 1.21 and 3.89 ± 1.28 D, the average initial DAP was 24.47 ± 0.81 and 24.23 ± 0.46 mm, the average keratometry was 42.77 ± 0.95 and 43.87 ± 0.93 D for Groups 1 and 2 , respectively.

Of the 30 patients in Group 1, two were excluded because they interrupted the use of eyedrops for more than 30 days, and one in Group 2 for not returning for the final examination.

Regarding the data collected at the beginning of the study and 2 years later, there was a significant reduction in myopia progression in Group 1 (of 0.43 ± 0.19 and 1.24 ± 0.37 D for Groups 1 and 2, respectively, $p < 0.05$), and there was also a significant reduction in the DAP in Group 1 (of 0.19 ± 0.09 and 0.48 ± 0.12 mm for Groups 1 and 2, respectively , $p < 0.05$). There was no difference in K for both Groups. Regarding the average ages, there were no significant differences in refractions and DAP between males and females.

Figure 1 shows the reduction of myopia progression in Group 1.

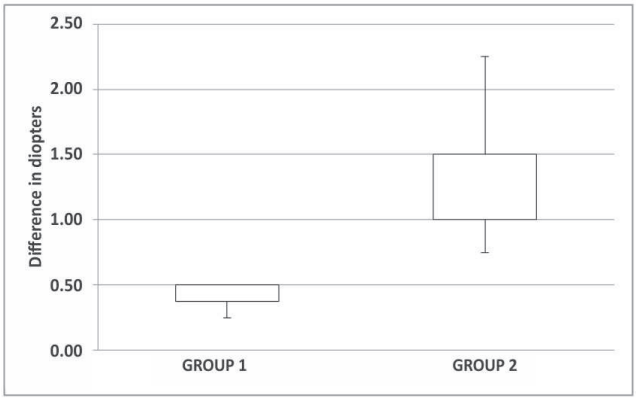

Figure 1: Differences between refractive measures in 2 years (in Diopters)

Figure 2 shows the reduction in DAP growth in Group 1.

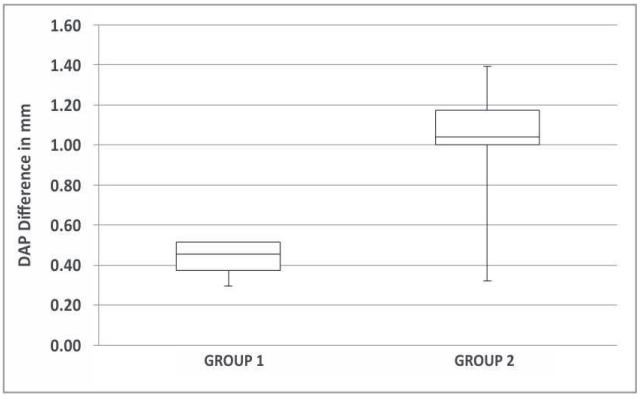

Figure 2: Differences between DAP measures in 2 years (in mm)

Figure 3 shows the distribution of differences in refractive measures during the two years of study.

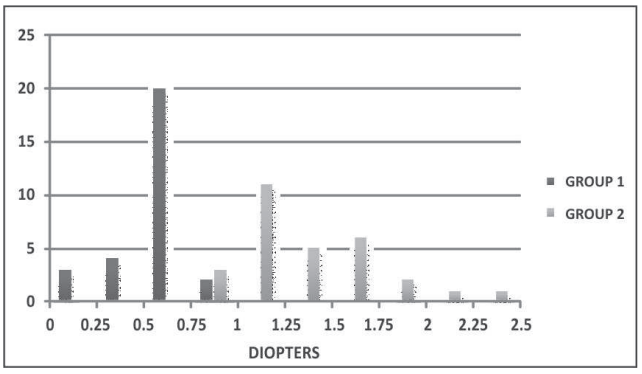

Figure 3: Distribution of differences between refractive measures in 2 years (in Diopters)

Discussion

The World Health Organization has considered the control of myopia as one of their five priorities for the coming years.[21] They took into account not only the financial impact, but also the increased risks of the complications of high myopia already reported in Asian countries.[22] Therefore, the decrease in myopia progression has remarkable clinical relevance due to the high risks of functional vision loss associated to pathological myopia.

There are some more current theories to explain the mechanism of action of atropine in decreasing DAP growth, such as the inhibition of muscarinic receptors of amacrine cells in the retinal medial periphery, the increase of intraocular dopamine by increased light input, but they have not yet been fully enlightened.[23,24]

The lowest dose of atropine in the world is the concentration of 0.01% used in the ATOM 2, but the ideal concentration was not determined in the present study, but rather the comparison of the results of the use of 0.5, 0.1 and 0.01%. The latter would be the placebo in this study, but surprisingly it revealed to the investigators good control, low side effects, and the absence of therapeutic rebound after interruption of medication.[14,16] Other previous studies have used atropine 0.025% with low rates of side effects reported as well.[18] The study considered as maximum acceptable dose 0.02%, and that could also bring greater changes in accommodation and pupillary diameter, and detected high levels of variation of accommodation amplitude among the results, not found in a previous study of these authors.[17] Some Asian studies have suggested that new concentrations greater than 0.01% may be more effective in controlling myopia.[25] The higher concentrations tended to saturate more the muscarinic receptors, thus having a greater therapeutic effect, as demonstrated in the present study with the 65% control of myopia progression in relation to the control group.

Several studies have indicated that exposure to sunlight leads to lower increases in DAP, thus decreasing the progression of myopia.[7,24,26] In the present study, the group treated did not use photosensitive lenses to filter sunlight, they only used multilayer anti-reflective lenses to reduce excessive intraocular UV rays, which are related to other important eye damage such as AMD.[27,28] As the progression of myopia may be associated to other ocular biometric factors, in order to suggest the use of atropine eyedrops in relation to the control of myopia, besides the refraction under cycloplegia, it is important to observe the regularity and stability of the corneal topography and the growth

of the dioptric power related to the growth of DAP, since the progression of myopia by increased corneal curvature is not controlled this way. In the present study, we achieved 60% less growth of DAP in the group treated, corroborating previous studies and suggesting that the control may also relate to the lens.[14,20]

This study has some limitations, as the control group not using the same type of lenses, not having a pre-treatment time to observe the progression of myopia, not being randomized and double-blind.

Conclusion

Atropine at low concentrations was effective in decreasing the progression of myopia in 65% of this population studied for 2 years. The concentration of 0.025% suggests to be more effective than 0.01%, and finally there is no need for photosensitive lenses.

The more children and youngsters being treated, the less they will suffer from myopia in adulthood, and the lower the risks of related complications they will have. However, studies with more participants and in several regions of Brazil could better demonstrate this fact.

References

1. Wu HM, Seet B, Yap EP, Saw SM, Lim TH, Chia KS. Does education explain ethnic difference in myopia prevalence? A population-based study of young adult males in Singapore. Optom Visc Sci. 2001;78(4):234-9.
2. Lin LL, Shih YF, Tsai CB, Chen CJ, Lee LA, Hung PT, Hou PK. Epidemiologic study of ocular refraction among schoolchildren in Taiwan in 1995. Optom Vis Sci. 1999;76(5):275-81.
3. Lam CS, Goldschmidt E, Edwards MH. Prevalence of myopia in local and international schools in Hong Kong. Optom Vis Sci. 2004;81(5):317-22.
4. Vitale S, Sperduto RD, Ferris FL. Increased prevalence of myopia in the United States between 1971–1972 and 1999–2004. Arch. Ophthalmol. 2009;127(12):1632-9.
5. Williams KM, Bertelsen G, Cumberland P, Wolfram C, Verhoeven VJ, Anastasopoulos E, et al. Increasing prevalence of myopia in Europe and the impact of education. Ophthalmology. 2015;122(7):1489-97.
6. Cui D, Trier K, Munk Ribel-Madsen S. Effect of day length on eye growth, myopia progression, and change of corneal power in myopic children. Ophthalmology. 2013;120(5):1074-9.
7. Rose KA, Morgan IG, Ip J, Kifley A, Huynh S, Smith W, Mitchell P. Outdoor activity reduces the prevalence of myopia in children. Ophthalmology. 2008;115(8):1279-85.
8. Li SM, Li SY, Kang MT, Zhou Y, Liu LR, Li H, et al. Near Work Related Parameters and Myopia in Chinese Children: the Anyang Childhood Eye Study. PLoS ONE. 2015; 10(8):e0134514.
9. Gimbel HV. The control of myopia with atropine. Can J Ophthalmol. 1973;8(4):527-32.
10. Bedrossian RH. The effect of atropine on myopia. Ophthalmology. 1979;86(5):713-7.
11. Chua WH, Balakrishnan V, Chan YH, Tong L, Ling Y, Quah BL, Tan D. Atropine for the treatment of childhood myopia. Ophthalmology. 2006;113(4):2285-91.
12. Aller TA. Clinical management of progressive myopia. Eye. 2014;28(2):147-53.
13. Huang J, Wen D, Wang Q, McAlinden C, Flitcroft I, Chen H,et al. Efficacy Comparison of 16 Interventions for Myopia Control in Children. A Network Meta-analysis. Ophthalmology. 2016; 123(4):697-708.
14. Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A, Tan D. Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for theTreatment of Myopia 2). Ophthalmology. 2012;119(2):347-54.
15. Tong L, Huang XL, Koh AL, Zhang X, Tan D, Chua WH. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. Ophthalmology. 2009;116(3):572-9.
16. Chia A, Chua WH, Wen L, Fong A, Goon YY, Tan D. Atropine for the treatment of childhood myopia: after stopping atropine 0.01%, 0.1% and 0.5%. Am J Ophthalmol. 2014;157(2):451-7.
17. Cooper J, Eisenberg N, Schulman E, Wang FM. Maximum atropine dose without clinical signs or symptoms. Optom Vis Sci.2013;90(12):1467-72.
18. Fang PC, Chung MY, Yu HJ, Wu PC. Prevention of myopia onset with 0.025% atropine in premyopic children. J Ocul Pharmacol Ther 2010;26(4):341-5.
19. Cunha CM, Queiroz FS, Santos Neto FR, Cunha JT, Correia RJB. Tolerância ao colírio de atropina 0,025%, sem lentes fotossensíveis. In Congresso CBO, Florianópolis. 2015. Arq Bras Oftalmol. 2015;78(4 Supl):25.
20. Cunha CM, Correia RJB, Cunha JT. Atropine to myopia control without photosensitive lens. In Global Pediatric Ophthalmology Congress, London. 2016. J Clin Exp Ophthalmol. 2016;7:3(suppl).
21. World Health Organization: Global Initiative for the Elimination of Avoidable Blindness: action plan 2006-2011, 2007.
22. Ohsugi H, Ikuno Y, Shoujou T, Oshima K, Ohsugi E, Tabuchi H. Axial length changes in highly myopic eyes and influence of myopic macular complications in Japanese adults. PLoS ONE. 2017;12(7):e0180851.
23. Mcbrien NA, Arumugam B, Gentle A, Chow A, Sahebjada S. The M4 muscarinic antagonist MT-3 inhibits myopia in chick: evidence for site of action. Opthalmic Physiol Opt. 2011;31(5):529-39.
24. Ashby RS, Schaeffel F. The effect of bright light on lens compensation in chicks. Invest Ophthalmol Vis Sci. 2010;51(10):5247-53.
25. Chuang AY. How to effectively manage myopia. Taiwan J Ophthalmol. 2017;7:4-7.
26. Guo Y, Liu LJ, Xu L, Lv YY, Tang P, Feng Y, Meng M, Jonas JB. Outdoor activity and myopia among primary students in rural and urban regions of Beijing. Ophthalmology. 2013;120(2):277-83.
27. Queiroz JM, Queiroz Junior JM, Queiroz FJC. Degeneração macular relacionada à idade: considerações histopatológicas. Rev Bras Oftalmol. 2010;69(6):400-6.
28. Dutot M, Rambaux L, Warner M, Rat P. Modulation du stress oxidant par la myrtille riche en polyphenoic sur in modèle de cellules humaines de rétine. J Fr Ophtalmol. 2008;31(10):975-80.

Corresponding author:
Celso Marcelo Cunha
Av: Miguel Sutil, 8000, Santa Rosa Tower, 2° andar, sala 208.
Cuiabá - MT - CEP 78040 400
E-mail: celsomcunha@terra.com.br