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Efficacy of atropine 0.01% for the treatment of childhood myopia in European patients

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ABSTRACT.

Purpose: **To evaluate the efficacy and safety of atropine 0.01% in slowing myopia progression in European paediatric patients.**

Methods: **Retrospective, medical records review study. Medical charts of paediatric patients with a myopia progression > 0.5 D/year treated with atropine 0.01% for at least 1 year were included. Patients receive a complete ophthalmic examination before and 12 months after initiation of atropine treatment. A group of myopic untreated children serves as a control group. The rate of myopia progression at baseline and 12 months after treatment with atropine was evaluated. The rate of myopia progression in treated and untreated patients was also compared. Adverse events were recorded.**

Results: **Medical records of 52 treated and 50 control subjects were analysed. In the atropine group, the mean rate of myopia progression after 12 months of treatment (−0.54 ± 0.61 D) was significantly slower compared with the baseline progression (−1.20 ± 0.64 D; $p < 0.0001$) and to the progression in the control group (−1.09 ± 0.64; $p < 0.0001$). The responders patients were 41/52 (79%), whereas 11/52 patients (21%) showed a progression > 0.50 D despite treatment. The only adverse event was temporary photophobia in five patients (9.6%), severe adverse events were not reported, and none of the patients discontinued the treatment.**

Conclusion: **Low-dose atropine significantly slowed the rate of myopia progression in European paediatric patients with a favourable safety profile.**

Key words: atropine – children – European – progressive myopia

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Introduction

Myopia is considered a significant public health concern nowadays and has been included among the priorities in the 'Vision 2020' initiative by the World Health Organization's Global Initiative for the Elimination of Avoidable Blindness (Pararajasegaram 1999).

The prevalence of myopia is rapidly growing worldwide. Recent reviews estimated that 2.5 billion people will have myopia by 2020 (Morgan et al. 2012) and approximately half of the world population will be myopic by 2050 with 10% of them affected by high myopia (Holden et al. 2016).

The prevalence of myopia is growing in both Asian and West countries (Tay et al. 1992; Vitale et al. 2009). In the United States, myopia affects approximately 40% of the adult populations (Vitale et al. 2009) and a rising prevalence has been reported in European area (Williams et al. 2015) and even in Australia, a low myopia prevalence area, where a fourfold increase in the prevalence of myopia was observed throughout the past century (McCarty & Taylor 2000).

In Asian countries, the prevalence of myopia has rapidly grown in the past decades, and today in the urban areas, up to 90% of high-school students are affected by myopia and up to 20% are affected by high myopia (Lin et al. 2004). In addition to the epidemiologic and social burden, myopia is a known risk factor for a sight-threatening condition as retinal detachment, myopic macular degeneration and glaucoma (Mitchell et al. 1999; Pan et al. 2012). Several treatments have been investigated for the control of myopia including the topical use of atropine. Although in the past decades clinical studies investigated the role of atropine in controlling myopia (Bedrossian 1971; Kelly et al. 1975; Yen et al. 1989), was not until the Atropine for the Treatment of childhood Myopia (ATOM) studies were performed that we had convincing evidence on the efficacy of the high dose 1% (ATOM1) (Chua et al. 2006) and the lower doses 0.5, 0.1 and 0.01% (ATOM2) (Chia et al. 2012) atropine in slowing childhood myopia.

A Cochrane review of the interventions to control myopia progression in children concluded that atropine was the only treatment showing a significant efficacy compared with placebo (Walline et al. 2011).

Two different meta-analyses (Huang et al. 2016; Gong et al. 2017) confirmed the conclusions of the Cochrane review showing that atropine 0.01% have comparable efficacy to the higher dose of atropine with the advantage of a lower incidence of adverse events and the absence of rebound effect after discontinuing the treatment.

Finally, the recent report of American Academy of Ophthalmology states that level I evidence supports the use of atropine for the control of myopia progression (Pineles et al. 2017).

As the majority of the studies were carried out with Asian descent subjects, few data are available so far about the efficacy of atropine in slowing myopia in European population.

Since data from the 5-year follow-up of the ATOM2 study (Chia et al. 2016) were available (September 2015), we started to treat children showing progressive myopia with a daily application of atropine 0.01%. This retrospective study aimed to evaluate the efficacy and the safety of atropine 0.01% in slowing myopia progression in European children over 1 year of treatment.

Materials and Methods

We conducted a retrospective review of electronic medical records of children referred to Eye Clinic, San Giuseppe Hospital (Milan, Italy), for progressing myopia (> 0.50 D/year) from September 2015 to September 2016 and treated with topical atropine 0.01%.

Criteria for inclusion in this analysis were as follows: patients aged 5–16 years with a myopic progression of at least 0.5 D in the past year (documented by cycloplegic refractive examinations), treatment with atropine 0.01% once in the evening for at least 12 months, best-corrected visual acuity ≥ 0.2 (Snellen acuity) in each eye, European descent and good adherence to the treatment reported by the relatives at our adherence assessment monitoring (less than 5 forgotten doses/month). Exclusion criteria were as follows: myopia related to collagen and systemic syndromes, and myopia due to buphthalmos; ocular surgery 6 months before or during the treatment period; the use of concomitant ocular medication during the treatment period; a diagnosis of developmental disorders as well as a diagnosis of ocular diseases, such as, strabismus, congenital cataract, glaucoma, corneal opacity, optic neuropathy, uveitis and ocular tumour; and previous use of treatment with a potential role in slowing myopia such as orthokeratology, contact lenses and progressive addition spectacle lenses. The efficacy was evaluated by the comparison of the mean change in refractive error (spherical equivalent, SE, assessed under cycloplegic condition) in the past 12 months before treatment with the mean change in refractive error in the 12 months after atropine treatment was started.

We included in the analysis a control group of myopic children with SE progression > 0.5 D/year referred to our Eye Clinic before 2015 and meeting the inclusion and exclusion criteria of the study, except that they have not been treated with atropine. Patients with a follow-up of at least two years were considered and analysed as a control group. The study and data accumulation were carried out with approval from the Institutional Ethics Committee (San Giuseppe Hospital, MultiMedica) and adhered to the tenets of the Declaration of Helsinki.

Study design

Every patient treated with atropine routinely received a complete ophthalmic examination before treatment and 6 and 12 months after initiation of treatment. Distance best-corrected visual acuity values were reported in decimal, as in clinical practice.

Refractive error was evaluated under cycloplegic condition at baseline and 12 months after treatment was started in the treated group and at 12 months interval in the control group using Nikon Retinomax 2 autorefractor (Nikon, Tokyo, Japan). The same device has been used throughout the study period. The SE was calculated as sphere plus + 1/2 cylinder. The rate of myopia progression was calculated by subtracting the SE at baseline from the SE 1 year before the treatment (rate of progression before treatment) and SE after 12 months of treatment from the SE at baseline (rate of progression during treatment). We similarly calculate the rate of progression in the control group throughout 24 months. Treated patients were considered responders if SE progression was < 0.50 D after 12 months of treatment and non-responders if SE progression continued even under atropine use. Adverse events were assessed during the examination. Also, patients and parents were asked for any adverse events eventually occurred during the treatment. The same pharmacy compounded all eye drops bottles.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and range [min; max]. They were then compared between treated and controls by using the t-test (normally distributed variables) or the non-parametric Wilcoxon test (not normally distributed variables). Differences in myopic progression rate were evaluated by using the non-parametric Wilcoxon signed rank test.

All statistical analyses were performed using SAS software (SAS version 9.4, Cary, NC, USA). Statistical significance was set to the conventional p-value < 0.05.

Results

Patients

Among the paediatric patients referred to Eye Clinic, San Giuseppe Hospital from September 2015 to September 2016, 52 Caucasian children (27/52 male, 52%) treated with atropine met the inclusion criteria and were included in the analysis, and 50 children (26/50 male, 52%) were included in the control group. The mean age was 9.7 ± 2.3 years (range 5–14 years) and 12.1 ± 2.9 years (range 6–16 years) in the atropine and the control group, respectively.

At baseline, the mean SE was 3.0 ± 2.23 D and 2.63 ± 2.68 D, and the mean best-corrected distance visual acuity was 0.58 ± 0.28 and 0.65 ± 0.14 in the atropine and in the control group, respectively. Only age was statistically different between the two groups (p-value < 0.0001). All the other demographic characteristics were comparable between groups (Table 1).

Efficacy

Table 2 shows the myopic progression rate in the studied subjects. In the treated group, the mean rate of myopia progression was significantly lower

Table 1. Demographics and baseline characteristics of patients.

	Atropine 0.01 group	Control group	p-value
Patients, *n*	52	50	
Gender, *n* (%)			
Male	27/52 (52%)	26/50 (52%)	0.9938
Female	25/52 (48%)	24/50 (48%)	
Age (years), mean ± SD [range]	9.7 ± 2.3 [5–14]	12.1 ± 2.9 [6–16]	<0.0001
Ethnicity, *n* (%)			
European	52/52 (100%)	50/50 (100%)	1.0000
Spherical equivalent (D), mean ± SD	−3.00 ± 2.23	−2.63 ± 2.68	0.1117
Distant BCVA (decimal), mean ± SD	0.58 ± 0.28	0.65 ± 0.14	0.3261
Subjects with high myopia (>6D), *n* (%)	8/52 (15%)	5/50 (10%)	0.4493

Table 2. Myopic progression rate.

Myopic progression rate (D/year)	Atropine 0.01 group	Control group	p-value
Baseline (between visit 1 and visit 2), mean ± SD	−1.20 ± 0.64	−0.80 ± 0.38	<0.0001
After 12 months (from visit 2), mean ± SD	−0.54 ± 0.61	−1.09 ± 0.64	<0.0001
p-value	<0.0001	<0.0001	

after 1 year of follow-up if compared with the mean myopia progression rate 12 months before treatment (−0.54 ± 0.61 D versus −1.20 ± 0.64 D; p-value < 0.0001). The responders patients were 41, (79%) whereas 11 patients (21%) showed a progression > 0.50 D despite treatment. Among the 11 non-responders, none showed high myopia (> 6 D), and none were less than 6 years old at baseline (mean SE 3.24 ± 1.32; mean age 9.0 ± 2.34, results not shown). The small sample size of these subgroups did not allow a statistical analysis of these data.

In the control group, untreated subjects showed a significantly faster progression compared with patients using atropine. The mean rate of progression during the first and the second year of follow-up was −0.80 ± 0.38 D and −1.09 ± 0.64 D; the mean rate of progression in the control subjects through the second year was significantly higher if compared with those of patients treated with atropine (−1.09 D versus 0.54 D, p-value < 0.0001). The final mean best-corrected distance visual acuity was 0.81 ± 0.2 in the treated subjects and 0.70 ± 0.21 in the control group.

Safety

Among 52 patients receiving atropine, five patients (9.6%) complained of photophobia; nevertheless, these symptoms were temporary and not severe enough to warrant discontinuing treatment. The use of atropine was overall very well tolerated. None of the treated patients needed photochromatic progressive glasses or single-vision photochromatic glasses. No systemic adverse events were reported.

Discussion

In this retrospective study, we investigated the efficacy of atropine 0.01% for the control of progressive myopia in European children. In our practice, we adhered to the indication of the ATOM2 study (Chia et al. 2012) (we only extended the age from 5 to 16 years), so we can consider this study as the first report on the application of the ATOM2 study protocol in myopic European children. Similarly to the ATOM2 study, we compared the mean SE change before and after treatment with atropine. The rate of myopia progression after 12 months of daily use of atropine was significantly lower compared with the rate of progression before starting the treatment.

The 0.54 D of myopia progression in the treatment period in our study was similar to the 0.42 D of progression reported after the 12 months of atropine in the ATOM2 study (Chia et al. 2012). In agreement with other reports, we noted that a percentage of patients (21%) showed progression despite treatment with atropine. This result is close to the 24% of progressing patients in the 0.01% group of the ATOM2 study. It has been reported that some patients seem to be non-responder to a low dose of atropine (Chia et al. 2012; Clark & Clark 2015). In these non-responder patients, an approach with a higher dose of atropine should be balanced with potential side-effects and considered.

We introduce a control group of patients with progressive myopia referred to our Clinic before the routine use of atropine. The subjects in the control group showed a slower rate of myopia progression at baseline compared with the atropine group. This could be partially explained as subjects in control group are slightly older, and it is known that myopia tends to decrease its progression in children of older age, together with the slightly lower percentage of subjects with high myopia in the control group. It is worth to note that despite the faster baseline progression, the treated subjects during the 12 months of treatment showed a significantly slower progression when compared to the progression throughout both the first and the second year of follow-up in the control group.

The first attempts to prevent myopia progression using atropine date back to the 60s (Otsuka 1967), and first randomized clinical trials started in the late 80s (Yen et al. 1989; Shih et al. 1999, 2001). However, only with the publication of the ATOM1 study the role of the atropine was fully elucidated. This randomized trial published in 2006 involved 400 Chinese children and confirmed that atropine is a powerful tool to control myopia with treated subjects showing a 77% decrease in the mean progression of myopia compared with placebo (Chua et al. 2006). The first studies (Yen et al. 1989; Shih et al. 1999, 2001), as well as the ATOM1 study (Chua et al. 2006), used atropine at the dose of 1%. At that concentration, atropine has been shown to be effective in slowing myopia progression (Chua et al. 2006); however, glare, photophobia and near reading difficulty were frequently reported (Chua et al. 2006; Yi et al. 2015) and limited a wide diffusion in clinical practice. In order to minimize clinical symptoms, lower doses of atropine have been explored from 0.5% to 0.01% (Chia et al. 2012). The

ATOM2 study was the first study exploring the efficacy of atropine 0.01% (Chia et al. 2012). The 5-year report of the ATOM2 study showed that 0.01% dose had a similar efficacy in slowing myopia progression compared with 0.1% and 0.5% over 24 months of treatment (phase 1 of the ATOM2 study), with the advantage of significant reduction of side-effects associated to pupil dilation and loss of accommodation (Chia et al. 2016). In addition, patients treated with atropine 0.01% did not show the rebound effect in the washout period (phase 2 of the ATOM2 study) like patients treated with atropine 0.1% and 0.5%. In the phase 3 (retreatment of progressing patients with 0.01%) of the ATOM2 study, only 24% of patients previously treated with atropine 0.01% needed retreatment compared with 59% and 68% in the 0.1% and in the 0.5% group, respectively, meaning that a significantly less proportion of patients were progressed in the 0.01% group. The conclusion of the 5-year report of the ATOM2 study was that atropine 0.01% was significantly more effective in slowing myopia progression with less visual side-effects compared with 0.1% and 0.5% dose (Chia et al. 2016).

To date, few studies investigated the efficacy of atropine in non-Asian subjects (Clark & Clark 2015; Polling et al. 2016; Diaz-Llopis & Pinazo-Durán 2018) and only two of them with atropine 0.01% (Clark & Clark 2015; Diaz-Llopis & Pinazo-Durán 2018).

In the study of Polling and coauthors, atropine was used at the higher concentration of 0.5%. Although myopia was adequately controlled, the frequency of adverse events was relevant to photophobia reported in 72% of subjects (Polling et al. 2016).

The study by Clark and coauthors was the first study analysing the efficacy of atropine 0.01% in a subgroup of non-Asian subjects (Clark & Clark 2015). The study was conducted in the United States and included 56 children of different ancestry (Asian, Caucasian, Hispanic, and African American). In this retrospective work, children treated with atropine 0.01% were compared with a control group. The Caucasian patients were 15 (54% of the 28 treated patients). One significant difference between this study and our work is that in the former, cycloplegic refraction was not routinely performed and change of SE was calculated based on non-cycloplegic manifest refraction. Other difference is the larger sample size of our study, including 52 Caucasian treated patients (Clark & Clark 2015).

The second work on the efficacy of atropine 0.01% in a Caucasian population is a recently published randomized Spanish study comparing the rate of myopia progression of 100 treated patients with 100 untreated subjects (Diaz-Llopis & Pinazo-Durán 2018). In this study, atropine significantly slowed myopia progression progression compared with control group (-0.14 ± 0.35 versus -0.65 ± 0.54, respectively)

There are some differences between this study and our work. Patients in the Spanish study were older compared with the current study as inclusion age was 9–12 years. Inclusion criteria of study by Diaz-Llopis and colleague were similar to the ATOM 1 study (Chua et al. 2006), as children with myopia from -0.50 to -2.00 D were included regardless of the rate of progression. In our study, we included children with progressive myopia, accordingly with the ATOM 2 study criteria (Chia et al. 2012). Another difference to be commented is that in work by Diaz-Llopis and colleague (Diaz-Llopis & Pinazo-Durán 2018), there was a high rate of dropout in the treatment group (53.5%), so authors upgraded the number of included children during the follow-up, trying to balance the two group by 'dynamic randomization'. This may have biased the inclusion process and the final results of the study.

Atropine is a non-selective muscarinic receptor antagonist. The exact mechanism by means atropine would arrest myopia is not clearly understood so far. In animal models, atropine showed to prevent the development of myopia effectively (McBrien et al. 1993; Schwahn et al. 2000). A block of accommodation has been postulated; however, atropine was able to prevent myopia even in animals that do not have accommodation mechanism (Saw et al. 2002). In addition, striated ciliary muscles of animals like chickens showed nicotinic acetylcholine receptors rather than muscarinic receptor, so in these animals, the block of the muscarinic receptor by atropine would not be useful to inhibit accommodation (McBrien et al. 1993). Diether et al. recently proved that atropine could inhibit the development of experimental myopia in chickens in a dose-dependent fashion. Although the exact mechanism is unknown, findings of this study suggest that atropine seems to inhibit the synthesis of glycosaminoglycans in scleral chondrocytes, suggesting that the scleral tissue could be the target of atropine (Diether et al. 2007). Among the limitations of this work, the retrospective design of the study carries the attendant limitations of any retrospective analysis and do not allow an evaluation of the safety of the drug as accurate as in a clinical trial; however, adverse events were recorded in the medical charts and had been analysed in our report. The 9.6% of patients complaining of transient photophobia is close to the 6.3% of photophobia reported in a recent meta-analysis (Gong et al. 2017) and was the only adverse event reported by the treated patient. The axial length was not analysed. Randomized clinical trial as the ATOM1 and ATOM2 studies (Chua et al. 2006; Chia et al. 2012) reported axial length and suggested that the control of myopia progression seems to depend on slowing in axial growth. The retrospective nature of this study reflects the real-life clinical practice. As this measurement is not routinely performed during clinical examination, axial length data are lacking in our analysis. Moreover, differently from clinical trials, we did not have any effective method to control adherence to the therapy; nevertheless, only patients with less than 5 forgotten doses/month were included in the analysis. This study did not include patients older than 16 years. Further studies might address the efficacy of low-dose atropine even in patients in the late teens with progressive myopia. As this retrospective chart review study analysed patients who were still under treatment with atropine, this work cannot provide information about the myopia progression after cessation of treatment. Further analysis will elucidate about the rebound effect in European children treated with low-dose atropine. Finally, our study population was a relatively homogeneous group of European children aged 5–16 years with a rate of progression of 0.5D of SE in the past year, without any other ocular or

systemic relevant disease, so the interpretation of our findings should be restricted to similar patients.

Open questions remain about the optimal time of starting and cessation treatment, as well as the approach for patients still progressing under atropine 0.01%, and we hope this study will encourage further research on this topic and these open issues.

Besides, growing literature recently is debating about the role of outdoor time in the control of the myopia process, suggesting that spending time in outdoor activities may play a role in slowing myopia process, so future studies should integrate and consider the role of outdoor time in combination with treatment such as atropine (Rose et al. 2008; He et al. 2015; Ramamurthy et al. 2015).

In conclusion, atropine can be considered the only approach for the control of myopia currently evidence-based. Large, randomized studies (Chua et al. 2006; Chia et al. 2012) and recent meta-analysis (Walline et al. 2011; Huang et al. 2016; Gong et al. 2017; Pineles et al. 2017) have demonstrated that daily use of topical atropine can prevent further myopia progression in children, and pooled evidence suggests that the low-dose atropine 0.01% is effective as higher atropine concentration with a more favourable safety profile.

As our current knowledge on the efficacy of atropine 0.01% is substantially based on data coming from Asian subjects (Chua et al. 2006; Chia et al. 2012), and as a difference in efficacy between White and Asian people has been postulated (Li et al. 2014), we think that our findings on the efficacy of low-dose atropine in European descent children could be of clinical interest. This study highline as even in European patient low-dose atropine is an effective and safe treatment and should be considered in myopic subjects meeting the inclusion criteria of our work.

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