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Myopia: Efficacy of 1% Atropine in Retarding Progression

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Abstract

Purpose: To determine the efficacy of 1% atropine eye drops in control of myopia progression. **Methods:** This was a Case control study, conducted at the Mohsin Family Health Clinic, Block-16, Federal B Area, Karachi, during January 2018 to December 2019. A total of 194 (97 cases and 97 controls) cases were included in the study by the calculation of online software openepi.com. The Treatment Group was given 1% atropine eye drops while Control Group received no treatment. The follow-up of all the cases was carried out according to the follow-up schedule for a total period of one year. All the demographic data, clinical findings and the follow-up results were recorded on a proforma designed for the study, and the results were tabulated. **Results:** A total of 194 children age 6-15 with best corrected visual acuity 6/6 were recruited in this study. Half of the children were included in treatment group who received once a day application of 1% atropine eye drops at bedtime. The other half received no treatment and were taken as control group. Mean spherical equivalent refraction (SER) at baseline was 2.93±0.69 of Treatment Group and 2.98±0.61 of control group with insignificant P-value of 0.461. After 1-year treatment statistically significant difference with P-value 0.001, was observed with SER 3.37±0.91 in Treatment Group and 3.69±0.94 in control group. **Conclusion:** Atropine 1% eye drops is well tolerated and is found efficacious in controlling myopia progression.

Keywords: Atropine 1%, Muscarinic antagonist, Myopia control, Spherical equivalent refraction.

INTRODUCTION

Myopia has taken an epidemic form over the last few decades [1]. It has now become a serious ocular disorder affecting as many as 37% of Asian children [2]. Myopia possesses a long list of serious ocular complications like cataract, glaucoma, peripheral retinal degenerations, disc abnormalities, chorio-retinal degenerations, lacquer cracks, retinal neovascularization, and maculopathy that may lead to blindness [3]. Besides having physical and psychological effect on children, myopia poses considerable socio-economic impact over the family. In view of global epidemic of myopia, several risk factors linked to myopia have been identified causing its development and progression/stabilization. These factors have been studied for their potential for causing visual impairment in myopia.

Correction of Myopia Evaluation Trial (COMET) examined associated factors of myopia and found ethnicity and number of myopic parents to have association with myopia stabilization as well as age and amount of myopia [4]. The 2008-2012 Korean National Health and Nutrition Examination Survey demonstrated influence of parental refractive error in myopia prevalence [5]. Inverse relationship has been described by Jones A *et al*. and Rose KA between myopia development and bright light and with sports and number of outdoor activities [6-7]. In context of bright light exposure, role of dopamine in myopia development is studied which is released secondary to light exposure [8]. Rod stimulation secondary to dim light is also being investigated due to the correlation of more myopic errors with increased time in mesopic light [9]. In addition to identification of risk factors, different measures have been adopted for treating myopia. Atropine has been used since long and found to be the only pharmacological agent that has demonstrated efficacy to slow the myopia progression/stabilization [10-11].

The mechanism of myopia control with atropine is not fully understood. Influence of atropine on biological mechanisms within different ocular sites particularly in retina and sclera have been hypothesized [12]. Atropine sulfate is anticholinergic nonselective, muscarinic acetylcholine receptor antagonist. Acetylcholine has been identified to control ocular growth [13]. Atropine block the action of acetylcholine at the muscarinic receptors. Large number of muscarinic receptors are found in different ocular tissues like cornea, scleral fibroblasts, choroid, iris, ciliary muscles and ciliary body, epithelium of crystalline lens, retinal amacrine cells and retinal pigment epithelium. Cellular proliferation of primary scleral fibroblast is regulated by epidermal growth factor receptor which has demonstrated reduced activity by atropine in animal model [12]. Beside muscarinic receptors, atropine has found to have potential interactions with other non-muscarinic receptors within the ocular tissues [14].

Atropine in higher concentrations (0.5%-1%) has proven efficacy for myopia control [15]. A meta-analysis of fort four studies by Prousali E *et al.* [16] described atropine to be well tolerated with use of different concentrations. Another meta-analysis by Huang J *et al*. [10] found no specific dose dependency and efficacy with use of different concentrations of atropine. Atropine for the treatment of myopia 1 (ATOM1) study determined the efficacy of 1% atropine [13]. Blurred vision and hypersensitivity reaction are the common side effects reported with the use of 1% atropine. Blurred vision was usually secondary to pupil dilatation and temporary lack of accommodation. Use of different concentration 1%, 0.5%, 0.1% and 0.01% of atropine in Atropine for the treatment of myopia 2 (ATOM2) study found 1% atropine to have a higher efficacy of 78% and in 20% of poor responders to lower concentrations [17]. Variable results to different concentrations of atropine may be secondary to different amount of iris pigmentation [18]**.** However, no uniform treatment has been described due to presence of heterogenicity and other factors. Association of myopia with serious ocular pathologies particularly with high degrees of refractive error, have prompted to find strategies to slow down its progression. This developed a curiosity to design a study to find the efficacy of 1% atropine on myopia progression in our outpatient population.

METHODS

This case control study with non-probability purposive sampling technique was carried out at Mohsin Family Health Clinic, Block-16 Federal B Area Karachi. A prior Ethical approval was taken from the institutional Review Committee of the Institute and study was conducted as per principles of Helsinki Declaration of 1975 as revised in 2000. Records of patients were traced out from January 2017 to December 2019. Study duration was from January-2018 to December-2019, Sample size was calculated from online software openepi.com with statistical conditions of 95% confidence interval and 5% margin of error. Comparing proportions of two independent sample in which prevalence of myopia was cited as 37% total required sample calculated was 194. Two equal groups of patients were formed (97-cases and 97-controls). Patients receiving 1% atropine drops were included in “Treatment Group”. The other group was not given any medicine and taken as “Control Group”. Inclusion criteria were age between 6 to 15 years of either gender, baseline spherical equivalent refraction (SER) from − 0.25 to − 8.0D after cycloplegic refraction, astigmatism (if present in either eye) ≤ − 2.0D after cycloplegic refraction and having best corrected visual acuity of 6/6. Exclusion criteria were patients having history of ocular trauma and/or ocular surgery, suffering from any ocular disorder other than myopic refractive error, suffering from any systemic disorder having effect on ocular structure like Stickler syndrome, Marfan syndrome, suffering from ocular structural abnormalities like keratoconus, lenticonus, spherophakia, microspherophakia, and anisometropia of more than 2D.

Data Collection Procedure

After considering the inclusion and exclusion criteria, the parents were briefed about the study and informed consent was obtained. Visual assessment and detailed ophthalmic examination were performed. Cycloplegic refraction was done with duochrome test. Spectacle correction of single vision glasses was given as it is described not to affect myopia progression [19]. Both eyes were included in the study. Atropine 1% eye drops was prescribed to Treatment Group with frequency of one drop in each eye once every night before sleep. Punctal occlusion and lid closure for five minutes after instillation of drops, was advised to minimize systemic effects of atropine. All patients were examined after one day and then one week to find any untoward side effect of atropine and intraocular pressure (IOP) was measured with applanation tonometer. The patients were then followed up for one year after every three months. Refraction and IOP measurements were documented at each visit. All adverse effects were documented to find the safety profile of 1% atropine over use of one year. Compliance to treatment was also confirmed from parents. Photophobia was overcome by prescribing photochromic glasses when reported.

Outcome Measures

Outcome measures were primary and secondary efficacy variable as defined by the FDA advisory committee [20]. Primary efficacy variable was progression of myopia from baseline SER expressed in dioptre (D)/year. Secondary efficacy variable was Clinically significant worsening of myopia of at least = or > than -0.75 D of SER from baseline. Study was done in accordance with principles of the Helsinki Declaration of 1975, as revised in 2000.

STATISTICAL ANALYSIS

Analysis was performed by software Statistical Package for Social Sciences (SPSS) version 23.0. Continuous variables were presented as mean and standard deviation. All categorical variables are shown as frequency and percentages. Paired *t*-test was used as a test of significance to compare pre- and post-treatment progression. Effect of age, gender, and the baseline progression on the effectiveness of atropine eye drops were analyzed. P-value < 0.05 was taken statistically significant.

RESULTS

A total of 194 children (97-cases and 97-controls) were recruited in this study. Ten children of Treatment Group were excluded due to the reason of developing severe allergic dermatitis (n=1), showing non-compliance to treatment (n=3) and lost to follow-up (6) making a total number of 87 subjects. Eight children from control group were excluded for irregular follow up (n=2) and lost to follow-up (n=6) making a total of 89 subjects. Result of 352 eyes of 176 children were therefore used for final assessment.

Mean age of the participants was 10.24 years with ±1.65 SD. Age group was further subdivided into two groups, Group 1 between age 6-10 years and Group 2 having age 11-15 years. Female: Male ratio was 1:0.67 with 109 female and 67 males. Both groups were compared at baseline. Progression of myopia was monitored in both groups over a period of one year. Effect of atropine on myopia progression was assessed in Treatment Group and its comparison was made with the Control Group to find significance. Baseline SER of Treatment and Control Groups have shown insignificant difference with a P-value of 0.461. Statistically significant difference was found in mean SER of both groups at 1-year with P-value 0.001 presented in Table 1 showing change in SER of 0.44 in treatment eyes and 0.73 in controls. Effect of treatment on myopia is assessed in detail and is presented in Figure 1. Statistically significant difference was observed with P-value <0.001. Out of a total of 352 eyes, high increase SER>-1.0D was observed in only 3.4%(n=12) treated eyes compared to 9.6%(n=34) Control eyes. Moderate increase of SER>-0.75 was shown in only 10.22%(n=36) of treated eyes compared to 32.38%(n=114) of control group. Minimal increase of SER= or<-0.25 D was observed in 28.4%(n=100) eyes of Treatment Group and 7.38%(n=26) of control group. Improvement in SER+0.25D was demonstrated in 7.38%(n=26) eyes with treatment in comparison to only 4(1.13%) of control group with P-value < 0.001. Age and gender of the sample were also analysed. The children were divided in two groups based on age. Group 1 comprised of children age between 6-10 years with 45(51.7%) in Treatment Group and 47(52.8%) in Control Group whereas Group2 comprised of age 11-15 years with 42(48.3%) in Treatment Group and 42(47.2%) in control group. There were 59.77%(n=52) female and 40.22%(n=35) males in Treatment Group and 64.04%(n=57) female and 35.95%(n=32) male in Control Group. Effect of treatment was compared with age and gender to find significance presented in Table 2.

Table 1: Mean SER at baseline and after 1 year

Group	Mean SER ± SD at Baseline	P-value	Mean SER ± SD at One Year	P-value	Change in SER
Treatment (n=174)	2.93±0.69	0.461	3.37±0.91	0.001	0.44
Control (n=178)	2.96±0.61		3.69±0.94		0.73

Independent sample t-test was applied for significance
P-value ≤0.05 considered to be statistically significant

Table 2: Comparison of Age and Gender with SER

	Age Groups						Gender Groups					
SER	Treatment		P-value	Control		P-value	Treatment		P-value	Control		P-value
	6-10 years	11-15 years		6-10 years	11-15 years		Male	Female		Male	Female	
High SER >-1.0	0	6	0.044	5	13	0.11	8	2	0.044	14	4	0.846
	0.00%	14.30%		10.4%	29.5%		15.4%	5.7%		24.6%	12.5%	
Moderate SER>-0.75	8	10		35	25		17	4		37	23	
	17.80%	23.80%		72.9%	61.4%		32.7%	11.4%		64.9%	71.9%	
Minimal SER = or < -0.25	29	21		6	3		22	21		5	4	
	64.40%	50.00%		14.6%	6.8%		42.3%	60.0%		8.8%	12.5%	
Improvement SER + 0.25 change	8	5		1	1		5	8		1	1	
	17.80%	11.90%		2.1%	2.3%		9.6%	22.9%		1.8%	3.1%	
Total	45	42		47	42		52	35		57	32	
	100.0%	100.0%		100.0%	100.0%		100.0%	100.0%		100.0%	100.0%	

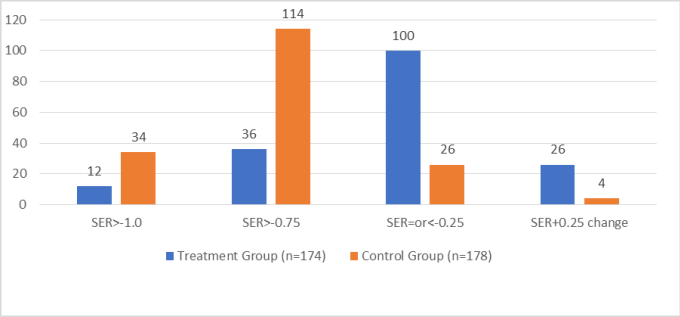

Figure 1: Effect of atropine on myopia progression (Eyes)

DISCUSSION

The results of our study demonstrated beneficial effect on myopia after the use of 1% atropine treatment in controlling progression. The main output requirement of our study was to find progression of myopia from baseline SER expressed in dioptre (D)/year after the use of atropine 1%. Highly significant difference with P-value 0.001, in myopia progression was found between Treatment and Control Group. The Control Group showed increase of 0.73D while in Treatment Group, it was 0.44D. Myopia reduction by 0.29D/year of our study is comparable to 0.160D/year (95% CI: -0.293-0.613) as reported by Song Y-Y *et al.* [21]. Similar results have also been described by Yi S *et al* with a decrease of 0.32±0.22D from baseline [22]. A

decrease by 0.63 ± 0.59D (p = 0.007) in treated eye and increase of -0.72 ± 0.65D in control eyes (p<0.001) is documented by Lin L *et al* in the result of their pilot study [23]. Rate of progression was found to be reduced to -0.2D/year after atropine therapy, in a study by Kothari M and Rathod V [18]. Results of meta-analysis of forty-four studies by Prousali E *et al.* [16] demonstrated 0.78D decrease in refraction after 1-year use of 1% atropine drops. Mean progression of myopia was only -0.28+/-0.92D in atropine treated eyes as compared to -1.20+/-0.69 D of control in study by Chua HW *et al*[13]. Secondary efficacy variable of our study was Clinically significant worsening of myopia of =or> than -0.75D of SER. The results of our study presented in Figure 1. Worsening of myopia was seen in 83.14% eyes (n=148) in Control Group while it was found only in 27.56% of eyes (n=48) demonstrating efficacy of 1% atropine in controlling myopia progression.

No gender difference was observed in our study as regards to efficacy of atropine drops with insignificant P-value of 0.084. Similarly, age did not show statistically significant difference with the treatment P-value 0.044. Similar results were found in the study conducted on Indian cohort showing insignificant gender-based and age relation with efficacy of atropine [18].

Atropine 1% is found to be well tolerated in our study as has been described in other studies [13, 16, 18, 21-24]. All adverse events were recorded comprising of photophobia, allergic dermatitis, conjunctivitis, difficulty in reading, headache, eye pain, ocular irritation, and redness. No serious side effects were observed except for one participant who developed severe allergic dermatitis that demanded exclusion from the study as was also reported in a study of Prousali E *et al.* [16]. Photophobia and blurred near vision are the usual side effects after the use of atropine particularly with higher concentrations. The temporary paralysis of accommodation, pupillary dilatation and UV exposure are the main reason for limiting its use. Photophobia reported in our study was successfully controlled by prescription of photochromic glasses. Use of photochromic, UV coatings and progressive lenses are described to alleviate these issues [18]. There are also concerns about retinal damage after prolong use of atropine. However, safety profile of atropine in this regard has been demonstrated by Cooper J. *et al* evidenced by normal electroretinographic results after prolong use of atropine [24].

Selection of 1% atropine in our study was based on safety profile reports from different studies and with dose-response relationship and efficacy with higher concentration [15-18, 23-25]. Promising results were described in ATOM1 study conducted by Chua *et al*. for the control of myopia with 1% atropine with nearly 77% reduction in myopic progression after 2 years use [13]. A review of myopia control with atropine by Tran HDM *et al*. [15] describe high dose atropine (0.5%-1%) to be most effective in controlling myopia progression.

Beside the side effects, beneficial use of 1% atropine is limited by rebound effect [25]. Findings of ATOM 2 studies demonstrated efficacy of lower concentrations of atropine with least side effects and lower incidence of rebound. However, patients having high degrees with a family history of myopia, and poor responders to lower concentration, require higher concentrations [25]. To overcome the difficulties with lower concentration, it is suggested to start treatment with lower strength followed by stepwise increase in dose, depending upon the response and to continue therapy for longer period [15]. Stepwise tapering after stabilization of myopia is further suggested to prevent rebound [26].

Atropine treatment for myopia is still not used widely due to lack of uniformity of management plan. There is a need to control myopia progression owing to the incidence of serious retinal complications that increases above 2 diopters of myopia [24]. Keeping myopia below 2 dioptres would be beneficial in reducing these risks. It has been estimated by Brennan [27] that if myopia progression is reduced by 33%, it will result in myopia reduction by 73% above 5D and if the progression rate is further reduced to 50%, it will result in reduction of myopia to 90%. The worldwide increase of myopia has become a public health concern and needs to be dealt on priority to preserve vision and to reduce the socio-economic burden of individual and society as whole.

CONCLUSION

Atropine 1% is well tolerated and effective for control of myopia progression. Further research is required to develop a uniform management plan particularly to control rapid progression of myopia with the use of 1% atropine eye drops.

Conflict of interest:

There exist no conflict of interest and no source of funding.

Author contribution:

1. **Mashhood-uz-Zafar Farooq:** Concept, study design, protocols, manuscript writing, review, and final approval of manuscript.
2. **Shama Mashhood:** Study design, review of manuscript, data analysis, result writing, final approval of manuscript.
3. **Sana Adeeba:** Study design, review of manuscript, data handling, final approval of manuscript.
4. **Raffat Rasool:** Study design, result writeup, literature search, review of manuscript and final approval.
5. **Mahmood Akhter Rana:** Data collection, data entry, literature search, review of manuscript and final approval.
6. **Syed Safdar Zamir Rizvi:** Study design, review of manuscript, final approval
7. **Muhammad Faisal Fahim:** Data handling, result writing.

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